SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:
Tenezil 5 (Tablets)
Tenezil 10 (Tablets)
Tenezil 20 (Tablets)

COMPOSITION:
Each Tenezil 5 tablet contains: 5 mg enalapril maleate.
Each Tenezil 10 tablet contains 10 mg enalapril maleate.
Each Tenezil 20 tablet contains 20 mg enalapril maleate.

Excipients:
Ethanol, ferric oxide red, ferric oxide yellow, lactose monohydrate, magnesium stearate, maize starch, sodium hydrogen carbonate and talc.

Each Tenezil 5 tablet contains sugar (129, 8 mg lactose monohydrate).
Each Tenezil 10 tablet contains sugar (124, 6 mg lactose monohydrate).
Each Tenezil 20 tablet contains sugar (117.8 mg lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION:
A 7.1.3 Vascular medicines - other hypotensives

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
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.

Pharmacokinetic properties:
Absorption:
Enalapril is absorbed from the gastro-intestinal tract and has an oral bioavailability of approximately 60 %. 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 to 4 hours and has a plasma half-life of up to 11 hours.

Distribution:
Enalaprilat is 50 to 60% bound to plasma proteins.

Metabolism:
Enalapril maleate is a prodrug that is hydrolyzed by esterases in the liver to produce enalaprilat, the active dicarboxylic acid. Enalaprilat is a potent inhibitor of ACE with a K_i of 0, 2 nM.

Elimination:
Elimination is mainly via the kidneys (60 %) as intact enalapril, as well as the active enalaprilat. The remainder is eliminated in the faeces.

INDICATIONS:
TENEZIL is indicated in:
Hypertension:
Treatment of hypertension.

Heart failure:
TENEZIL is indicated for the treatment of symptomatic congestive cardiac failure, usually in combination with digoxin and diuretics.

Asymptomatic left ventricular dysfunction:
Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection function ≤ 35 %).

CONTRAINDICATIONS:
- Hypersensitivity to any of the ingredients of TENEZIL.
- 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.
- 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 (see "INTERACTIONS").
- Porphyria (or motivate if not contraindicated).
- Lithium therapy: Concomitant administration with TENEZIL may lead to toxic blood concentrations of lithium (see "INTERACTIONS").
- Pregnancy and lactation (see "PREGNANCY AND LACTATION").
- The concomitant use of TENEZIL with aliskiren-containing products is contraindicated in patients with mellitus or renal impairment (GFR < 60 mℓ/min/1, 73 m^2) (see "WARNINGS & SPECIAL PRECAUTIONS" AND "INTERACTIONS").
- Concomitant use of fluoroquinolones with ACE inhibitors/ Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment (see "WARNINGS & SPECIAL PRECAUTIONS" AND "INTERACTIONS").

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving TENEZIL, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see "CONTRAINDICATIONS and PREGNANCY AND LACTATION").

TENEZIL should be used with caution in the following conditions:
Symptomatic hypotension:
This was seen in uncomplicated hypertensive patients. In hypertensive patients receiving TENEZIL, hypotension is more likely to occur if the patient has been volume depleted e.g. by diuretic therapy, dietary salt reduction, dialysis, diarrhoea, or vomiting (see "INTERACTIONS" and "SIDE EFFECTS").
Heart failure patients with or without associated renal insufficiency have been known to suffer from symptomatic hypotension.

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 TENEZIL 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 infraction 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 TENEZIL. If hypotension becomes symptomatic, a reduction of dose or discontinuation of TENEZIL may be necessary.

Aortic or Mitral Valve Stenosis/ Hypertrophic Cardiomyopathy:
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Acute myocardial infarction:
In acute myocardial infarction, treatment with TENEZIL 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 TENEZIL may need to be withdrawn (see "CONTRAINDICATIONS").

In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Hypotension in acute myocardial infarction-treatment with TENEZIL 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 TENEZIL should be withdrawn.

Acute Kidney Injury (AKI):
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 "CONTRAINDICATIONS"). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

Renal function impairment:
Patients with renal insufficiency may require reduced and/or less frequent doses of TENEZIL (see "DOSAGE AND DIRECTIONS FOR USE"). 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 "CONTRAINDICATIONS"). This is especially likely in patients with renal insufficiency.

Some patients with no apparent pre-existing renal disease have developed an increase in blood urea and serum creatinine when TENEZIL has been given concomitantly with a diuretic. Dosage reduction of TENEZIL and/or discontinuation of the diuretic may be required.
Decreased elimination of TENEZIL resulting in an increased risk of hyperkalaemia. These patients may require lower doses (see "CONTRAINDICATIONS").

Kidney Transplantation:
There is no experience regarding the administration of TENEZIL in patients with a recent kidney transplantation.

Treatment with TENEZIL is therefore not recommended.

Hepatic failure:
Rarely, ACE inhibitors 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 who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

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. 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.

Autoimmune Diseases:
Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma: Increased risk for development of neutropenia or agranulocytosis.

Hypersensitivity/angioedema:
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including TENEZIL. In such cases, TENEZIL 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.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy such as subcutaneous epinephrine solution 1:1 000 (0,3 mℓ to 0,5 mℓ) should be administered promptly.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see "CONTRAINDICATIONS").
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema.

Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of enalapril. Treatment with enalapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see "INTERACTIONS").

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see "INTERACTIONS"). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during hymenoptera desensitisation:
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily with-holding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis:
Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Hypoglycaemia:
Diabetic patients treated with oral antidiabetic medicines or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see "INTERACTIONS").

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

Surgery/anaesthesia:
In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
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, intercurrent 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 drugs associated with increases in serum potassium (e.g., heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. If concomitant use of enalapril and any of the above-mentioned medicine is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see "INTERACTIONS").

Lithium:
The combination of lithium and enalapril is generally not recommended (see "INTERCATIONS").

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 TENEZIL and aliskiren is therefore contraindicated (see "CONTRAINDICATIONS"). TENEZIL should not be used concomitantly with aliskiren (see "CONTRAINDICATIONS").

Paediatric use:
TENEZIL has not been studied in children.

***Ethnic differences*:**
As with other angiotensin converting enzyme inhibitors, 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.
Effects on ability to drive and use machines:
TENEZIL may make you feel dizzy or drowsy, or cause headaches. If it affects you in this way, do not drive, operate machinery, or do anything that requires you to be alert or until you know, how TENEZIL affects you.

Lactose:
TENEZIL contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TENEZIL.

TENEZIL contains lactose monohydrate, which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:
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 "CONTRAINDICATIONS", "WARNINGS AND SPECIAL PRECAUTIONS").

Potassium sparing diuretics or potassium supplements:
ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g., spironolactone, eplerenone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see "WARNINGS AND SPECIAL PRECAUTIONS").

Medicines increasing the risk of angioedema:
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see "CONTRAINDICATIONS" and "WARNINGS AND SPECIAL PRECAUTIONS").
Concomitant use of ACE inhibitors with racecadotril, MTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see "WARNINGS AND SPECIAL PRECAUTIONS").

Other Antihypertensive therapy:
The combination of TENEZIL 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.
Concomitant use of these medicines may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Diuretics (thiazide or loop diuretics):
With loop, thiazide, or related diuretics – "First dose hypotension" may occur (see "DOSAGE AND DIRECTIONS FOR USE").

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see "WARNINGS AND SPECIAL PRECAUTIONS"). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

The combination of TENEZIL with beta-adrenergic blocking medicines and methyldopa or calcium entry blockers potentiates the hypotensive effects of TENEZIL.

Ganglionic blocking medicines or adrenergic blocking medicines, combined with TENEZIL, should only be administered with careful observation of the patient.

Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see "WARNINGS AND SPECIAL PRECAUTIONS").

Tricyclic antidepressants/Antipsychotics/Anaesthetics/Narcotics:
Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see "WARNINGS AND SPECIAL PRECAUTIONS").

Serum potassium:
In patients with renal failure, the administration of TENEZIL 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 medicine is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Non-steroidal anti-inflammatory medicines (NSAIDs) including acetylsalicylic acid ≥ 3g/day:
Non-steroidal anti-inflammatory medicines (NSAIDs) – reduce the antihypertensive effects of TENEZIL. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with TENEZIL.

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 or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, 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. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

Serum lithium:
The lithium elimination may be reduced with increases in serum lithium concentrations reported (see "CONTRAINDICATIONS").

Mammalian target of rapamycin (mTOR) inhibitors:
Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see "WARNINGS AND SPECIAL PRECAUTIONS").

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 TENEZIL.

Neprilysin Inhibitors:
Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see "WARNINGS AND SPECIAL PRECAUTIONS"). 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 TENEZIL therapy. TENEZIL therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see "WARNINGS AND SPECIAL PRECAUTIONS").

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics:
Epidemiological studies have suggested that concomitant administration of ACE inhibitors 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 (see "WARNINGS AND SPECIAL PRECAUTIONS").
Alcohol:
Alcohol enhances the hypotensive effect of ACE inhibitors.

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

Ciclosporin:
Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended

Heparin:
Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see "CONTRAINDICATIONS").

PREGNANCY AND LACTATION:
Pregnancy:
The use of TENEZIL is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take TENEZIL during pregnancy (see "CONTRAINDICATIONS"). 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 TENEZIL should be stopped immediately and if appropriate, alternative therapy should be started. 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. TENEZIL 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 TENEZIL during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see "CONTRAINDICATIONS").

Lactation:
Enalapril and enalaprilat are excreted in breast milk but their effect on the breastfeeding infant has not been determined. Therefore the use of TENEZIL is not recommended in women breastfeeding their babies (see "CONTRAINDICATIONS").

DOSAGE AND DIRECTIONS FOR USE:
The absorption of TENEZIL is not influenced by food, thus it may be administered before, during or after meals.

Essential hypertension:
The initial dose is 10 to 20 mg administered once daily.
Mild hypertension – recommended initial dose is 10 mg daily.
Other degrees of hypertension – recommended initial dose 20 mg daily.
Usual maintenance dose 20 mg once daily.
The dose may be adjusted according to the needs and response of the individual patient.

Renovascular hypertension:
Blood pressure and renal function, in such patients, may be particularly sensitive to ACE-inhibitors. It is therefore recommended that initiation of therapy should be at a lower dose (5 mg or less).
The dose may then be adjusted according to the needs and response of the individual patient.

Most patients may be expected to respond to one 20 mg tablet taken once daily.
Caution is recommended in patients with hypertension who have recently been treated with diuretics.

Concomitant diuretic therapy in hypertension:
Symptomatic hypotension may occur following the initial dose of TENEZIL. This is more likely to occur in patients who are currently being treated with diuretics. Caution is recommended because these patients may be volume or salt depleted. It is recommended that diuretic therapy be discontinued 2 to 3 days prior to initiation of therapy with TENEZIL. If this is not possible, the initial dose of TENEZIL should be low (5 mg or less) in order to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the response of the individual patient.

Dosage in renal Insufficiency:
It is generally recommended that the intervals between the administration of TENEZIL should be prolonged and/or the dosage reduced.

Renal status	Creatinine clearance (mℓ/min)	Initial dose (mg/day)
Mild impairment Moderate impairment	< 80 > 30	5

Heart failure/asymptomatic left ventricular dysfunction:
The administration of TENEZIL should be done under close medical supervision to determine the initial effect on the blood pressure. In the absence of symptomatic hypotension or following effective management thereof, the dosage of TENEZIL may be carefully titrated upwards, towards the usual maintenance dose of 20 mg per day, given as a single dose or two divided doses, as best 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 was effective in reducing mortality.

Blood pressure and renal function should be closely monitored, before and after starting treatment with TENEZIL (see "WARNINGS AND SPECIAL PRECAUTIONS"), because hypotension and consequent renal failure have occurred.

In patients taking diuretics, the dosage should be reduced, if possible, before initiation of therapy with TENEZIL.
The appearance of hypotension following the initial dose of TENEZIL does not imply that hypotension will recur during chronic therapy with TENEZIL and does not preclude continued use of TENEZIL.
Serum potassium should also be monitored (see "INTERACTIONS").

SIDE EFFECTS

Blood and lymphatic system disorders:
Less frequent: Anaemia (including aplastic and haemolytic)
Frequency Unknown: Neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, and lymphadenopathy.

Immune system disorders:
Less frequent: Anaphylaxis and angioedema.

Endocrine disorders:
Frequency unknown: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders:
Less frequent: Hypoglycaemia.

Psychiatric disorders:
Frequent: Depression.
Less Frequent: Confusion, insomnia, nervousness, dream abnormality, sleep disorders.

Nervous system disorders:
Frequent: Headache, dizziness, syncope, taste alteration.
Less Frequent: Paraesthesia, vertigo, somnolence.

Eye disorders:
Frequent: Blurred vision.

Ear and labyrinth disorders:
Less frequent: Tinnitus.

Cardiac disorders:
Frequent: Chest pain, rhythm disturbances, angina pectoris, tachycardia.
Less frequent: Palpitations, myocardial infarction, or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients.

Vascular disorders:
Frequent: Hypotension (including orthostatic hypotension).
Less frequent: Flushing, orthostatic hypotension, Raynaud's phenomenon.

Respiratory, thoracic, and mediastinal disorders:
Frequent: Cough, dyspnoea.
Less Frequent: Rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:
Frequent: Nausea, diarrhoea, abdominal pain, taste alteration.
Less frequent: Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritation, dry mouth, peptic ulcer, stomatitis/aphthous ulcerations, glossitis, intestinal angioedema.

Hepatobiliary disorders:
Less frequent: Hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice).

Skin and subcutaneous tissue disorders:
Frequent: Rash, hypersensitivity/angioedema: angioedema of the face, extremities, lips, tongue, glottis and/or larynx.

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

Frequency unknown: A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis. Rash, photosensitivity, or other dermatologic manifestations may occur.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Muscle pains.

Renal and urinary disorders:
***Less frequent*:** Renal dysfunction, renal failure, proteinuria, oliguria.

Reproductive system and breast disorders:
***Less frequent*:** Impotence, gynaecomastia.

General disorders and administration site conditions:
***Frequent*:** Asthenia, fatigue.
***Less frequent*:** Muscle cramps, malaise, fever.

Investigations:
***Frequent*:** Hyperkalaemia, increases in serum creatinine.
Less frequent: Increases in blood urea, hyponatraemia, elevations of liver enzymes, elevations of serum bilirubin.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Symptoms of overdose:
Severe hypotension, electrolyte disturbances and renal failure.

Treatment of overdose:
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.

IDENTIFICATION:
Tenezil 5: oval, convex, white snap tab tablets, one side scored with markings of EN 5
Tenezil 10: oval convex, red brown snap tab tablets, one side scored with markings of EN 10
Tenezil 20: oval convex, orange snap tab tablets, one side scored with markings of EN 20

PRESENTATION:
Tenezil 5/10/20 tablets: are packed in aluminium/aluminium blisters. Blisters are placed into a cardboard carton. 10 tablets per blister strip. 3 blister strips per carton (30's)

STORAGE INSTRUCTIONS:
Store in a dry place at or below 25°C. Protect from light.
Do not remove blisters from the carton until required for use.
Do not remove tablets from container until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:
Tenezil 5: 33/7.1.3/0506
Tenezil 10: 33/7.1.3/0507
Tenezil 20: 33/7.1.3/0508

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Trinity Pharma (Pty) Ltd
106 16th Road,
Building 2,
Midrand

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date on the registration certificate of the medicine:
28 June 2000

Date of the most recently revised package insert as approved by Council:
04 April 2019

TRINITY PHARMA

Tel: 010 594 5610. Email: PV@kahmagroup.co.za