PROFESSIONAL INFORMATION

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SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

TENORETIC ® (100 mg Tablet)

TENORET ® **50** (50 mg Tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TENORETIC tablets contain 100 mg atenolol and 25 mg chlorthalidone.

TENORET 50 tablets contain 50 mg atenolol and 12,5 mg chlorthalidone.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

TENORETIC:

White, round, biconvex, film-coated tablets which are intagliated with 100 25 on one face and bisected on the reverse face.

TENORET 50:

White, round, biconvex, film-coated tablets which are intagliated with 50 12.5 on one face and bisected on the reverse face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of mild to moderate hypertension.

4.2 Posology and method of administration

Adults:

TENORET 50: One tablet daily.

TENORETIC: One tablet daily. There is little or no further fall in blood pressure with increased dosage, and where necessary another antihypertensive medicine, such as a vasodilator, may be added.

Patients can be transferred to TENORETIC/TENORET 50 from other antihypertensive treatments.

Elderly:

The normal dose should be reduced in elderly patients.

Children:

There is no paediatric experience with TENORETIC/TENORET 50. Therefore, these preparations are not recommended for children.

Renal failure:

In patients suffering from renal dysfunction, the normal dose should be reduced by decreasing the frequency of administration.

4.3 Contraindications

Neither TENORETIC nor TENORET 50 should be used:

- In pregnancy.
- During lactation.
- In patients with known hypersensitivity to either component.
- In patients with bradycardia.
- In patients with cardiogenic shock.
- In patients with hypotension.
- In patients with metabolic acidosis (e.g. in diabetes).
- In patients with severe peripheral arterial circulatory disturbances.
- In the presence of second degree or third-degree heart block.
- In patients with sick sinus syndrome.

- In patients with untreated phaeochromocytoma.
- After prolonged fasting.

Intravenous administration of calcium channel blockers with negative inotropic effects e.g. verapamil, should not be given concomitantly with TENORETIC/TENORET 50 or within 48 hours of discontinuation of TENORETIC/TENORET 50.

Special care should be taken with patients whose cardiac reserve is poor. TENORETIC/TENORET 50 should be avoided in cardiac failure, unless or until signs of failure are controlled with digoxin or diuretics.

Particular caution should be exercised with patients suffering from the following: asthma, bronchitis, chronic respiratory diseases.

4.4 Special warnings and precautions for use

TENORETIC/TENORET 50 may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. However, since atenolol is beta-1-selective, they may be used with utmost care.

TENORETIC/TENORET 50 may aggravate peripheral arterial circulatory disturbances and peripheral gangrene may be precipitated.

Due to their negative effect on conduction time, TENORETIC/TENORET 50 should only be given with caution to patients with first-degree heart block (see section 4.3).

TENORETIC/TENORET 50 may mask the signs of thyrotoxicosis.

In the peri-operative period it is generally unwise to reduce the dosage of TENORETIC/TENORET 50 therapy to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or of hypertension during the surgical or peri-operative period. A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery by TENORETIC/TENORET 50 therapy. Particular caution should be taken in this regard.

While taking TENORETIC/TENORET 50, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge. Such patients may be unresponsive to the usual dose of adrenaline used to treat allergic reactions.

Patients with a phaeochromocytoma require treatment with an alpha-adrenergic blocker.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy with TENORETIC/TENORET 50 should be gradual rather than abrupt, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

TENORETIC and TENORET 50 mask the symptoms of hypoglycaemia (i.e. may modify the tachycardia of hypoglycaemia). Chlorthalidone may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. Caution should be exercised with the concomitant use of TENORETIC/TENORET 50 and antidiabetic agents and blood glucose concentrations should be monitored in patients taking antidiabetic agents.

TENORETIC and TENORET 50 should be used with caution in patients with impaired hepatic or renal function, anuria or with a history of sensitivity to chlorthalidone.

The increase in airways resistance, which may occur in asthmatic patients, can usually be reversed by standard doses of bronchodilators. TENORETIC/TENORET 50 should be discontinued should an increase in airway resistance occur.

One of the pharmacological actions of TENORETIC/TENORET 50 is to reduce the heart rate. Bradycardia (usually less than 50-55 beats/minute) indicates that dosage should not be further increased. Should symptoms which may be attributable to a slow heart rate develop, the dose may be reduced.

Hypokalaemia may occur. Measurement of potassium levels is appropriate, especially in the older patient, those receiving digoxin for cardiac failure, those taking an abnormal (low in potassium) diet or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to dysrhythmias in

patients receiving digoxin.

Impaired glucose tolerance may occur, and caution must be exercised if chlorthalidone is administered to patients with a known pre-disposition to diabetes mellitus.

Hyperuricaemia may occur. Only a minor increase in serum uric acid usually occurs but in cases of prolonged elevation, the concurrent use of a uricosuric agent will reverse the hyperuricaemia.

Chlorthalidone, a sulphonamide, can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicines and other forms of interaction

Combined use of TENORETIC/TENORET 50 and calcium channel blockers with negative inotropic effects e.g. verapamil and diltiazem may lead to an exaggeration of negative inotropic effects, particularly in patients with impaired ventricular function and/or sino-atrial (SA) or atrio-ventricular (AV) conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither medicine should be given intravenously within 48 hours of discontinuation of the other.

Concomitant therapy with dihydropyridine calcium channel antagonists e.g. nifedipine, may increase the risk of hypotension. Cardiac failure may occur in patients with latent cardiac insufficiency.

Digoxin, in association with TENORETIC/TENORET 50, may increase atrioventricular conduction time.

TENORETIC/TENORET 50 may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If these medicines are co-administered, the TENORETIC/TENORET 50 should be withdrawn several days before discontinuing clonidine. If replacing clonidine by TENORETIC/TENORET 50 therapy,

the introduction of the latter should be delayed for several days after clonidine administration has stopped.

Class I antidysrhythmic medicines (e.g. disopyramide) and amiodarone may have potentiating effect on reduction of atrial-conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents e.g. epinephrine, may counteract the effect of TENORETIC/TENORET 50.

Concomitant use of prostaglandin synthetase inhibiting medicines e.g. ibuprofen and indomethacin, may decrease the hypotensive effect of TENORETIC/TENORET 50.

Preparations containing lithium should not be given with TENORETIC/TENORET 50 because the diuretic may reduce its clearance.

Caution must be exercised when using anaesthetic agents with TENORETIC/TENORET 50. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of TENORETIC/TENORET 50 with anaesthetic agents may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

It can be dangerous to administer TENORETIC/TENORET 50 concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and Class I antidysrhythmic agents such as disopyramide. Such interactions can have life-threatening consequences.

Special note:
Digitalisation of certain patients receiving long-term TENORETIC/TENORET 50 therapy can be valuable, particularly in those patients in whom congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the 2 medicines. Careful control of dosages and of the individual patient's response and notably the pulse rate is essential in this situation.

Chlorthalidone may enhance the toxicity of digitalis glycosides by depleting serum-potassium concentrations. The combination may enhance the neuromuscular blocking action of competitive muscle relaxants, such as tubocurarine. The combination may enhance the effects of antihypertensive agents, while postural hypotension associated with chlorthalidone may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids. Serum concentration of protein-bound iodine may increase without signs of thyroid disturbance. The patient should be carefully observed for signs of fluid electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

TENORETIC/TENORET 50 should not be given during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following undesirable effects, listed by body system, have been reported with the following frequencies: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, <1/100); Rare (≥ 1/10 000, < 1/1 000); Very rare (≤ 1/ 10 000) and not known (cannot be estimated from the available data):

Clinical trials:

System Organ Class	**Frequency**	**Event**
Blood and lymphatic system disorders:	Rare (≥ 1/10 000, < 1/1 000)	Purpura, thrombocytopenia, leucopenia (related to chlorthalidone)
Psychiatric disorders:	Uncommon (≥ 1/1 000, < 1/100)	Sleep disturbances of the type noted with other beta-blockers
	Rare (≥ 1/10 000, < 1/1 000)	Mood changes, nightmares, confusion, psychoses and hallucinations.

Nervous system disorders:	Rare (≥ 1/10 000, < 1/1 000)	Dizziness, headache, paraesthesia
Eye disorders:	Rare (≥ 1/10 000, < 1/1 000)	Dry eyes, visual disturbances
Cardiac disorders:	Common (≥ 1/100, < 1/10)	Bradycardia
	Rare (≥ 1/10 000, < 1/1 000)	Heart failure deterioration, precipitation of heart block
Vascular disorders:	Common (≥ 1/100, < 1/10)	Cold extremities
	Rare (≥ 1/10 000, < 1/1 000)	Postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present in susceptible patients, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders:	Rare (≥ 1/10 000, < 1/1 000)	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints
Gastrointestinal disorders:	Common (≥ 1/100, < 1/10)	Gastrointestinal disturbances (including nausea related to chlorthalidone)
	Rare (≥ 1/10 000, < 1/1 000)	Dry mouth
Hepatobiliary disorders:	Rare (≥ 1/10 000, < 1/1 000)	Hepatic toxicity including intrahepatic cholestasis, pancreatitis (related to chlorthalidone)
Skin and subcutaneous tissue disorders:	Rare (≥ 1/10 000, < 1/1 000)	Alopecia, psoriasiform skin reaction, exacerbation of psoriasis, skin rashes.
Reproductive system and breast disorders:	Rare (≥ 1/10 000, < 1/1 000)	Impotence
General disorders and	Common	Fatigue

administration site conditions:	(≥ 1/100, < 1/10)	
Investigations:	Common (≥ 1/100, < 1/10)	Related to chlorthalidone: Hyperuricaemia (may precipitate attacks of gout in susceptible patients), hyponatraemia, hypokalaemia, impaired glucose tolerance
	Uncommon (≥ 1/1 000, < 1/100)	Elevations of transaminase levels
	Very rare (≤ 1/ 10 000)	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

The following side-effects have been reported but frequencies are unknown:

Post-marketing experience:

System Organ Class	**Frequency**	**Event**
Blood and lymphatic system disorders:	Unknown	Agranulocytosis and thrombocytopenia in the adult may occur
Eye disorders:	Unknown	Choroidal effusion, acute myopia, acute angle-closure glaucoma (related to chlorthalidone).
Cardiac disorders:	Unknown	Congestive cardiac failure
Gastrointestinal disorders:	Unknown	Vomiting, diarrhoea
General disorders and administration site conditions:	Unknown	Chlorthalidone may cause photosensitivity and inflammation of the salivary gland
Psychiatric disorders:		Depression

In patients with severe congestive heart failure who are very oedematous, a low-salt syndrome may occur, particularly with large doses in conjunction with restricted salt in the diet. The urinary excretion

of calcium is reduced. Toxic effects such as hypochloraemic alkalosis and jaundice have been reported.

Note:

Adverse reactions to beta-blockers are more common in elderly patients, in patients with renal decompensation, and in patients who receive the medicine intravenously.

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. Health care providers 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

Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals.

Cases of mild overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Gastric lavage should be performed if within 4 hours of suspected overdose. Repeated activated charcoal is necessary in severe overdoses.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2,5-10 micrograms/kg/minute by intravenous infusion may be given, although larger doses may be required.

Excessive diuresis should be countered by maintaining normal fluid and electrolyte balance.

Bronchospasm can usually be reversed by bronchodilators. Bronchospasm should be treated by intravenous aminophylline, and heart failure with digitalis and diuretics.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3. Other hypotensives

Atenolol is a beta-blocker, which is beta-1-selective. Selectivity decreases with increasing dose. It does not possess membrane stabilising or intrinsic sympathomimetic activities. The mode of action of atenolol in the treatment of hypertension is unclear.

Chlorthalidone, a diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by which chlorthalidone reduces blood pressure is not fully known.

5.2 Pharmacokinetic properties

Co-administration of chlorthalidone and atenolol has little effect on the pharmacokinetics of either. Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40-50 %) with peak plasma concentrations occurring 2-4 hours after dosing. Approximately 60 % of an oral dose of chlorthalidone is absorbed from the gastrointestinal tract. Atenolol is only poorly bound to plasma proteins. Chlorthalidone is 75 % plasma protein bound. The t_{max} for atenolol is 3 hours and the t_{max} for chlorthalidone is 12 hours.

Metabolism of atenolol occurs to only a very minor extent and both atenolol and chlorthalidone are excreted predominantly via the kidney. The elimination half-life of atenolol is 6-9 hours and that for chlorthalidone is approximately 50 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TENORETIC/TENORET 50:

Tablet core:

Maize starch

Magnesium carbonate (heavy)

Gelatin

Sodium lauryl sulphate

Magnesium stearate

Coating:

Hypromellose

Glycerol

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

TENORETIC: 3 years

TENORET 50: 4 years

6.4 Special precautions for storage

Store at or below 25 °C

Protect from light and moisture.

6.5 Nature and contents of container

TENORETIC/TENORET 50: Blister packs of 30 tablets.

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park,

17 Georgian Crescent West,

Bryanston, Johannesburg, 2191,

South Africa

8 REGISTRATION NUMBERS

TENORETIC: M/7.1.3/106

TENORET 50: S/7.1.3/201

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

TENORETIC: 03 August 1981

TENORET 50: 06 July 1987

10 DATE OF REVISION OF THE TEXT

3 June 2022

Inclusion of Namibia + Botswana registration details (15-11-2010)

Tenoret 50	Tenoretic
NAMIBIA: NS2	NAMIBIA: NS2
Reg. No.: 90/7.1.3/00284	Reg. No.: 90/7.1.3/00285

Tenoret 50	Tenoretic
BOTSWANA: S2	BOTSWANA: S2
Reg. No.: B9311770	Reg. No.: B9311775