Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tenoretic 100mg/25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol 100 mg
Chlortalidone 25 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, film-coated tablet, intagliated 'Tenoretic' on one side and bisected on the reverse.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tenoretic 100 mg/25 mg Film-coated Tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on atenolol or chlorthalidone alone.

4.2 Posology and method of administration

Posology
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

Adults

The usual maintenance dose of Tenoretic 100 mg/25 mg Film-coated Tablets is one tablet daily. There is little or no further fall in blood pressure with increased dosage, and where necessary, another antihypertensive drug, such as a vasodilator, can be added. Patients can be transferred directly to Tenoretic 100 mg/25 mg Film-coated

Tablets from other antihypertensive treatments, with the exception of clonidine (see section 4.4).

Elderly
Dosage requirements are often lower in this age group.

Paediatric population
The use of Tenoretic 100 mg/25 mg Film-coated Tablets is not recommended in children. The safety and efficacy of Tenoretic 100 mg/25 mg Film-coated Tablets in children less than 18years has not yet been established.

Renal impairment
Due to the properties of the chlortalidone component, Tenoretic 100 mg/25 mg Film-coated Tablets has reduced efficacy in the presence of renal insufficiency. This fixed dose combination should thus not be administrated to patients with severe renal impairment (see section 4.3).

Hepatic impairment
Dose adjustments are not required in patients with hepatic impairment.

Method of administration
Tenoretic 100 mg/25 mg Film-coated Tablets are administered orally.

4.3 Contraindications

Tenoretic 100 mg/25 mg Film-coated Tablets should not be used in the following:

- hypersensitivity to the active substances (or to sulphonamide derived medicinal products) or to any of the excipients listed in section 6.1.
- bradycardia
- cardiogenic shock
- hypotension
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- second- or third-degree heart block
- sick sinus syndrome
- untreated phaeochromocytoma
- uncontrolled heart failure
- treatment with intravenous verapamil in the previous 48 hours
- hypokalaemia
- precoma associated with hepatic, renal or Addison's disease
- severe renal failure
- digitalis intoxication.

Tenoretic 100 mg/25 mg Film-coated Tablets must not be given during pregnancy or lactation.

4.4 Special warnings and precautions for use

Due to its beta-blocker component Tenoretic 100 mg/25 mg Film-coated Tablets:

- although contra-indicated in uncontrolled heart failure (see section 4.3) Tenoretic 100 mg/25 mg Film-coated Tablets may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

- may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Atenolol is a beta-1-selective beta-blocker; consequently the use of Tenoretic 100 mg/25 mg Film-coated Tablets may be considered although utmost caution must be exercised.

- although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), Tenoretic 100 mg/25 mg Film-coated Tablets may also aggravate less severe peripheral arterial circulatory disturbances.

- due to its negative effect on conduction time, caution must be exercised if it is given to patients with first-degree heart block.

- may modify the warning signs of hypoglycaemia as tachycardia, palpitation and sweating.

- may mask the cardiovascular signs of thyrotoxicosis.

- may mask the symptoms of thyrotoxicosis and of hypoglycaemia by inhibition of sympathetic nervous system. The effects of hypoglycaemic agents may be increased, but to a lesser extent than the non-cardioselective beta-blockers.

- will reduce heart rate, as a result of its pharmacological action. In the rare instances that symptoms may be attributable to the slow heart rate, the dose may be reduced.

- should not be discontinued abruptly in patients suffering from ischaemic heart disease since sudden withdrawal of beta-adrenoceptor blocking agents may result in increased frequency or severity of anginal attacks.

- may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.

- patients with bronchospastic disease should, in general, not receive beta blockers due to increasing in airways resistance. Atenolol is a beta1-selective beta-blocker; however this selectivity is not absolute. Therefore the lowest possible dose of Tenoretic 100 mg/25 mg Film-coated Tablets should be used and utmost caution must be exercised. If increased airways resistance does occur, Tenoretic 100 mg/25 mg Film-coated Tablets should be discontinued and bronchodilator therapy (eg salbutamol) administered if necessary. The betablocker should only be used with caution in patients with a family history of asthma.

- systemic effects of oral beta-blockers may be potentiated when used concomitantly with ophthalmic beta-blockers.

- in patients with phaeochromocytoma must be administered only after alfareceptor blockade. Blood pressure should be monitored closely.

- caution must be exercised when using anaesthetic agents with Tenoretic 100 mg/25 mg Film-coated Tablets. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

The metabolic effects of chlortalidone are dose-related and, at the low dose contained in Tenoretic 100 mg/25 mg Film-coated Tablets, are unlikely to be troublesome.

Tenoretic 100 mg/25 mg Film-coated Tablets are associated with only minor changes in potassium status. Total body potassium is unaltered on chronic therapy, and changes in serum potassium are minor and probably clinically unimportant. Thus, in cases of uncomplicated hypertension, concurrent potassium supplements should be unnecessary.

Due to its chlorthalidone component:

- plasma electrolyte should be periodically determined in appropriate intervals to detect possible electrolyte imbalance especially hypokalaemia and hyponatraemia.

- hypokalaemia and hyponatraemia may occur. Measurement of electrolytes is recommended, especially in the older patient, those receiving digitalis preparations for cardiac failure, those taking an abnormal (low in potassium) diet or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to arrhythmias in patients receiving digitalis.

- because chlortalidone may impair glucose tolerance and diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy test for glucosuria should be carried out at regular intervals.

- in patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma.

- hyperuricaemia or acute gout 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.

Adjustment of dosage of hypoglycaemic agents may be necessary if given to patients with uncontrolled or 'brittle' diabetes mellitus.

The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

Tenoretic 100 mg/25 mg Film-coated Tablets should only be used with caution in patients with controlled congestive cardiac failure or with a family history of asthma. Evidence of recrudescence of either condition should be regarded as a signal to discontinue therapy.

4.5 Interaction with other medicinal products and other forms of interactions

Due to atenolol:
Combined use of beta-blockers and calcium channel blockers with negative inotropic effects e.g. verapamil, diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), noradrenaline (norepinephrine) and isoprenaline may counteract the effect of betablockers.

Concomitant use of prostaglandin synthetase inhibiting drugs (e.g. ibuprofen, indometacin) may decrease the hypotensive effects of beta-blockers.

Caution must be exercised when using anaesthetic agents with Tenoretic 100 mg/25 mg Film-coated Tablets (see section 4.4).

Due to chlortalidone:
The chlortalidone component may reduce the renal clearance of lithium leading to increased serum concentrations. Dose adjustments of lithium may therefore be necessary.

Potassium depletion may be dangerous in patients receiving digitalis.

Due to combination product:
Concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of baclofen may increase the antihypertensive effect making dose adjustments necessary.

Administration in conjunction with other antihypertensives may require adjustment of dosage particularly in the case of catecholamine depleting agents such as reserpine or guanethidine.

Neurone blocking agents such as guanethidine, reserpine, diuretics and other antihypertensive agents, including the vasodilator group, will have an additive effect on the antihypertensive action of the drug.

The concomitant administration of this preparation with the cardiac glycosides, or non-depolarizing muscle relaxants may necessitate adjustment of the dosage of those drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy
Tenoretic 100 mg/25 mg Film-coated Tablets should not be given in pregnancy.

Breast-feeding
Tenoretic 100 mg/25 mg Film-coated Tablets must not be given during lactation.

Fertility
No data on fertility available.

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 use machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Tabulated list of adverse reactions
Tenoretic 100 mg/25 mg Film-coated Tablets are well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of its components.

The following undesirable effects, listed by body system, have been reported with the following frequencies: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from available data).

System Organ Class	Frequency	Adverse Drug Reaction

Blood and lymphatic system disorders	Rare	Purpura, thrombocytopenia, leucopenia (related to chlortalidone)
Psychiatric disorders	Uncommon	Sleep disturbances of the type noted with other beta blockers
	Rare	Mood changes, nightmares, confusion, psychoses and hallucinations
Nervous system disorders	Rare	Dizziness, headache, paraesthesia
Eye disorders	Rare	Dry eyes, visual disturbances
Cardiac disorders	Common	Bradycardia
	Rare	Heart failure deterioration precipitation of heart block
Vascular disorders	Common	Cold extremities
	Rare	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	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints
Gastrointestinal disorders	Common	Gastrointestinal disturbances (including nausea related to chlortalidone)
	Rare	Dry mouth
	Not known	Constipation
Hepatobiliary disorders	Rare	Hepatic toxicity including intrahepatic cholestasis, pancreatitis (related to chlortalidone)
Skin and subcutaneous tissue disorders	Rare	Alopecia, psoriasiform skin reaction, exacerbation of psoriasis, skin rashes
Musculoskeletal and connective tissue disorders	Not known	Lupus-like syndrome
Reproductive system and	Rare	Impotence

breast disorders		
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Related to chlortalidone: Hyperuricaemia, hyponatraemia, hypokalaemia, impaired glucose tolerance
	Uncommon	Elevations of transaminase levels
	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

Discontinuance of Tenoretic 100 mg/25 mg Film-coated Tablets should be considered if, according to clinical judgement, the well being of the patient is adversely affected by any of the above reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie.

4.9 Overdose

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion may be considered.

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 to 10 micrograms/kg/minute by intravenous infusion may be given.

Dobutamine, because of its positive inotropic effects could be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective and other diuretics
ATC Code: CO7C BO3.

Tenoretic 100 mg/25 mg Film-coated Tablets combine the antihypertensive activity of two agents, a beta-adrenergic receptor blocking agent (atenolol) and a diuretic (chlortalidone).

Atenolol:
Atenolol is $beta_1$ -selective (i.e. acts preferentially on $beta_1$ -adrenergic receptors in the heart). Selectivity decreases with increasing dose.

It has no intrinsic sympathomimetic activity and no membrane stabilising activity. Because of their inotropic effects, beta-blockers should be avoided in uncontrolled heart failure.

Atenolol reduces raised blood pressure by an unknown mechanism and also inhibits exercise-induced tachycardia and decreases plasma renin concentrations and free fatty acids.

Atenolol is the most cardioselective of the available beta-blockers in that it produces significantly less antagonism of the $beta_2$-effects. In addition, and in contrast to the non-selective agents, atenolol preserves the $beta_2$-bronchodilatory actions of inhaled isoprenaline. Furthermore prolongation of insulin-induced hypoglycaemia is less

unlikely to happen with cardioselective atenolol and at a daily dose of 50 mg no changes in plasma lipids are observed.

Atenolol is hydrophilic and relatively low concentrations are found in brain tissue leading to a very low incidence of CNS-related side effects in contrast with lipophilic beta-blockers.

Atenolol is effective and well tolerated in most ethnic populations although the responses may be less in black patients.

It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Chlortalidone:
Chlortalidone is a monosulfonamyl diuretic, which differs chemically from thiazide diuretics in that a double ring system is incorporated in its structure. It is an oral diuretic with prolonged action and low toxicity.

The diuretic effect of the drug occurs within 2 hours of an oral dose and continues for up to 72 hours. It produces copious diuresis and greatly increased excretion of sodium chloride.

At maximal therapeutical dosage, chlortalidone is approximately equal in its diuretic effect to comparable maximal therapeutic doses of benzothiadiazine diuretics.

The site of action appears to be the cortical dilating segment of the ascending lines of Henle's loop of the nephron.

The antihypertensive effects of Tenoretic 100 mg/25 mg Film-coated Tablets have been shown to be greater than those of atenolol or chlortalidone given alone. In patients with more severe hypertension, Tenoretic 100 mg/25 mg Film-coated Tablets may be administered with other antihypertensives such as vasodilators.

5.2 Pharmacokinetic properties

Atenolol:
In man absorption of atenolol following an oral dose of Tenoretic 100 mg/25 mg Film-coated Tablets is rapid and consistent but incomplete. Approximately 35% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the faeces. Peak atenolol blood levels of approximately 300 ng/ml are reached between 2 and 4 hours after ingestion and these vary only three-fold between subjects. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Atenolol is not significantly bound to plasma proteins and, in spite of this, and because of its high degree of hydrophilicity it has a low volume of distribution of about 0.7 l/kg. There is a very low concentration of atenolol in the brain. Atenolol has been shown to cross the placental barrier and it accumulates in breast milk without detriment to the neonate.

Atenolol is eliminated by renal excretion with a half-life of 5-7 hours which is not altered after chronic administration but does alter in renal insufficiency closely correlated with glomerular filtration rate. Accumulation of atenolol may occur in patients with a glomerular filtration rate less than 15 ml/min.

Atenolol is removed by haemodialysis.

The degree of beta-blockade is linearly related to the logarithm of the atenolol blood concentration but there is little correlation with antihypertensive effects.

Co-administration with chlortalidone in Tenoretic 100 mg/25 mg Film-coated Tablets does not affect the systemic availability of atenolol.

Chlortalidone:
In man absorption of chlortalidone following an oral dose of Tenoretic 100 mg/25 mg Film-coated Tablets is relatively slow but consistent. Peak chlortalidone blood levels of approximately 950 ng/ml are reached between 8 and 16 hours after ingestion and these vary only four-fold between subjects. There is no significant hepatic metabolism of chlortalidone.

Approximately 75% of a chlortalidone dose is bound to plasma proteins and 58% of the drug is bound to albumin. This is caused by an increased affinity of chlortalidone for erythrocyte carbonic anhydrase.

An average volume of distribution of 7.6 l/kg has been reported.

Chlortalidone has been shown to cross the placental barrier and to accumulate in breast milk without detriment to the neonate.

Chlortalidone is eliminated unchanged by renal excretion with a half-life of the order of 60 hours which is not altered after chronic administration but does alter in renal insufficiency.

Co-administration with atenolol in Tenoretic 100 mg/25 mg Film-coated Tablets does not affect the systemic availability of chlortalidone.

5.3 Preclinical safety data

Atenolol and Chlortalidone are drugs on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Maize Starch
Heavy Magnesium Carbonate
Gelatin
Sodium Laurilsulfate
Magnesium Stearate

Film Coating
Hypromellose
Glycerol
Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package. Keep the blister in the outer carton.

6.5 Nature and contents of container

PVC/aluminium foil blister strips (box of 28 tablets).

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1019/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th May 1979

Date of last renewal: 9th September 2007

10 DATE OF REVISION OF THE TEXT

January 2019