Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tenoret 50mg/12.5mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol 50 mg
Chlortalidone 12.5 mg
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, biconvex, film-coated tablet intagliated with the name 'Tenoret 50' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tenoret 50 mg/12.5 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 Tenoret 50 mg/12.5 mg Film-coated Tablets is one tablet daily. For patients who do not respond adequately to Tenoret 50 mg/12.5 mg Film-coated Tablets, the dosage may be increased to one tablet of Tenoretic.
Where necessary, another antihypertensive drug, such as a vasodilator, can be added.

Paediatric population
The use of Tenoret 50 mg/12.5 mg Film-coated Tablets is not recommended in children. The safety and efficacy of Tenoret 50 mg/12.5 mg in children less than 18years has not been established.

Renal impairment
Due to the properties of the chlortalidone component, Tenoret 50 mg/12.5 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
Tenoret 50 mg/12.5 mg film-coated Tablets are administered orally.

4.3 Contraindications

Tenoret 50 mg/12.5 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
– severe bradycardia
– cardiogenic shock
– hypotension
– metabolic acidosis
– severe peripheral arterial circulatory disturbances
– second- or third-degree atrioventricular block
– sick sinus syndrome
– untreated phaeochromocytoma
– uncontrolled or digitalis/diuretic refractory 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.

Tenoret 50 mg/12.5 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 Tenoret 50 mg/12.5 mg Film-coated Tablets:
–although contraindicated in uncontrolled heart failure (see section 4.3) may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor. Evidence of worsening heart failure should be regarded as a signal to discontinue therapy.

– may increase the number and duration of angina attacks in patients with Prinzmetals' angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Atenolol is a beta$_1$-selective beta-blocker; consequently the use of Tenoret 50 mg/12.5 mg Film-coated Tablets may be considered although utmost caution must be exercised.

– although contraindicated in severe peripheral arterial circulatory disturbances (see Contraindications), 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.

– will reduce heart rate, as a result of its pharmacological action.

In the rare instances when a treated patient develops symptoms which may be attributable to a 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 beta 1- selective beta- blocker; however this selectivity is not absolute. Therefore the lowest possible dose of Tenoret 50 mg/12.5 mg Film-coated Tablets should be used and utmost caution must be exercised. If increased airways resistance does occur, Tenoret 50 mg/12.5 mg Film-coated Tablets should be discontinued and bronchodilator therapy (e.g. salbutamol) administered if necessary. The beta-blocker 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 alfa-receptor blockade. Blood pressure should be monitored closely.

– caution must be exercised when using anaesthetic agents with Tenoret 50 mg/12.5 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.

Due to its chlortalidone 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 digital is 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.

– impaired glucose tolerance may occur 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.

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 atrioventricular 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 Tenoret 50 mg/12.5 mg Film-coated Tablets (see section 4.4).

Due to chlortalidone:
The chlorthalidone component may reduce the renal clearance of lithium leading to increased serum concentrations. Dose adjustments of lithium may therefore be necessary.
Adjustment of the dosage of hypoglycaemic agents may be necessary if given with uncontrolled or “brittle” diabetes mellitus.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Tenoret 50 mg/12.5 mg Film-coated Tablets must not be given during pregnancy.

Breast-feeding
Tenoret 50 mg/12.5 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
Tenoret 50 mg/12.5 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	Common	Cold extremities

disorders		
	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 breast disorders	Rare	Impotence
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 Tenoret 50 mg/12.5 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 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 effect could also 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: C07C B03

Tenoret 50 mg/12.5 mg Film-coated Tablets combine the antihypertensive activity of two agents, a beta-blocker (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.

Atenolol is without intrinsic sympathomimetic and membrane stabilising activities and, as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear.

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.

Atenolol is effective and well tolerated in most ethnic populations. Black patients respond better to the combination of atenolol and chlortalidone, than to atenolol alone.

The combination of atenolol with thiazide-like diuretics has been shown to be compatible and generally more effective than either drug used alone.

Chlortalidone
Chlortalidone, a monosulfonamyl diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by which chlortalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium.

5.2 Pharmacokinetic properties

Atenolol
Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40-50%) with peak plasma concentrations occurring 2-4 hours after

dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered. The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Chlortalidone
Absorption of chlortalidone following oral dosing is consistent but incomplete (approximately 60%) with peak plasma concentrations occurring about 12 hours after dosing. The chlortalidone blood levels are consistent and subject to little variability. The plasma half-life is about 50 hours and the kidney is the major route of elimination. Plasma protein binding is high (approximately 75%).

Co-administration of chlortalidone and atenolol has little effect on the pharmacokinetics of either.

Tenoret 50 mg/12.5 mg Film-coated Tablets are effective for at least 24h ours after a single oral daily dose. This simplicity of dosing facilitates compliance by its acceptability to patients.

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 Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Heavy magnesium carbonate
Maize starch
Sodium laurilsulfate
Gelatin
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 25ºC.
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

PA1019/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 1985

Date of last renewal: 09 September 2007

10 DATE OF REVISION OF THE TEXT

January 2019