SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tenoretic 100 mg/25 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 100 mg of Atenolol Ph. Eur. and 25 mg of Chlortalidone Ph.Eur.
For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

White

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of hypertension.

4.2 Posology and method of administration

Tenoretic film-coated tablets are administered orally.

Adults
One tablet daily. Most patients with hypertension will give a satisfactory response to a single tablet daily of 'Tenoretic'. 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.

Elderly
Dosage requirements are often lower in this age group.

Children
There is no paediatric experience with 'Tenoretic' tablets, therefore this preparation is not recommended for children.

Renal Impairment
In patients with severe renal impairment, a reduction in the daily dose or in frequency of administration may be necessary. (See Section 4.4).

4.3 Contraindications

'Tenoretic' tablets should not be used in patients with any of the following:

- known hypersensitivity to atenolol and chlorthalidone (or to sulphonamide derived medicinal products) or any other component of the product;
- 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.

'Tenoretic' tablets must not be given during pregnancy or lactation.

4.4 Special warnings and special precautions for use

Due to its beta-blocker component 'Tenoretic' 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.

- 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' tablets may be considered although utmost caution must be exercised.

- although contraindicated in severe peripheral arterial circulatory disturbances (See Section 4.3) 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 warning signs of hypoglycaemia as tachycardia, palpitation and sweating

- may mask the cardiovascular signs of thyrotoxicosis.

- in patients with pheochromocytoma Tenoretic must be administered only after alfa-receptor blockade. Blood pressure should be monitored closely

- 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.

- 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 used to treat the allergic reactions.

- may cause a hypersensitivity reaction including angioedema and urticaria.

'Tenoretic' tablets contain the cardioselective beta-blocker atenolol. Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, 'Tenoretic' tablets may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients, however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

The label and patient information leaflet for this product state the following warning:
"If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor".

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 hyponatriemia may occur. Measurement of potassium levels is appropriate, 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.

- caution must be exercised in patients with severe renal failure (See Section 4.2);

- because chlorthalidone may impair glucose tolerance 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 alteration in fluid and electrolyte balance may precipitate hepatic coma

- 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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Concomitant therapy with dihydropyridines eg. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

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.

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.
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Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs.

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

Due to chlorthalidone:

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

Caution must be exercised when using anaesthetic agents with 'Tenoretic' 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.

4.6 Pregnancy and lactation

Pregnancy:
'Tenoretic' tablets must not be given during pregnancy.

Lactation:
'Tenoretic' tablets must not be given during 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

‘Tenoretic' 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 (≥10%), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0.09%), very rare (<0.01%), not known (cannot be estimated from the available data):

<u>Blood and lymphatic system disorders:</u>

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.

Not known: Hypersensitivity reactions, including angioedema and urticaria.

Reproductive system and breast disorders:

Rare: Impotence.

General disorders and administration site conditions:

Common: Fatigue.

Musculoskeletal and connective tissue disorders:
Not known: Lupus-like syndrome

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' 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 is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475, website www.moh.gov.cy/phs , Fax: + 357 22608649

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 may 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-blocker 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

Beta-blocking agents, selective, and other diuretics.
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'Tenoretic' tablets combine the antihypertensive activity of two agents, a beta-blocker (atenolol) and a diuretic (chlortalidone).

Atenolol
Atenolol is $beta_1$ selective (ie 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-adrenoceptor blocking drugs, 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%).

Coadministration of chlortalidone and atenolol has little effect on the pharmacokinetics of either.

'Tenoretic' tablets are effective for at least 24 hours 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

Heavy Magnesium Carbonate, Maize Starch, Sodium Lauryl Sulphate, Gelatin, Magnesium Stearate, Hypomellose, Glycerol, Titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

4 years

6.4 Special precautions for storage

'Tenoretic' tablets should be stored below 25^0C.

Store in the original package. Keep the container in the outer carton.

6.5 Nature and contents of container

14 tablets

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd,
Silk Road Business Park
Charter Way
Macclesfield
Cheshire,
SK10 2NA
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

10556

9. DATE OF FIRST AUTHORISATION / RENEWAL

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10. DATE OF REVISION OF THE TEXT

17/11/2016