Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tenoretic 100 mg/25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol 100mg
Chlortalidone 25 mg

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Product imported from the UK:
Brown, film-coated tablets, imprinted Tenoretic on one side and an ‘S’ logo on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension:
The combination product may be suitable for use when satisfactory control of arterial blood pressure cannot be obtained with either a diuretic or a beta-blocking drug used alone.

Tenoretic 100 mg/25 mg Film-coated Tablets combine the antihypertensive effects of the cardioselective beta-blocker atenolol and the diuretic chlortalidone.

4.2 Posology and method of administration

Adults:
One tablet daily. Most patients with hypertension will have a satisfactory response to a single tablet daily of Tenoretic 100 mg/25 mg Film-coated Tablets. 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.

Children:
There is no paediatric experience with Tenoretic 100 mg/25 mg Film-coated Tablets; therefore, this preparation is not recommended for children.

Renal Failure:
Caution should be exercised in patients with renal failure. 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 100 mg/25 mg Film-coated Tablets should not be used in patients with any of the following:

- Known hypersensitivity to either component
- 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
- In the presence of hypokalaemia
- Precoma associated with hepatic, renal or Addison's disease
- Digitalis intoxication
- Asthma (see section 4.4).

Tenoretic 100 mg/25 mg Film-coated Tablets must not be used in patients who have received verapamil intravenously within 48 hours.

4.4 Special warnings and precautions for use

Special care should be taken with patients whose cardiac reserve is poor. Beta-blocking drugs should be avoided in overt heart failure. However, they may be used in patients whose signs of failure have been controlled.

One of the pharmacological actions of Tenoretic 100 mg/25 mg Film-coated Tablets is to reduce heart rate. In the rare instances that symptoms may be attributable to the slow heart rate, the dose may be reduced.

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.

As with other beta-blockers, treatment in patients with ischaemic heart disease should not be discontinued abruptly.

Tenoretic 100 mg/25 mg Film-coated Tablets 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.

Due to atenolol's negative effect on conduction time, caution must be exercised if it is given to patients with first-degree heart block.

Atenolol 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 beta1-selective beta-blocker; consequently the use of Tenoretic 100 mg/25 mg Film-coated Tablets may be considered although utmost caution must be exercised.

Atenolol may mask the signs of thyrotoxicosis.

Tenoretic 100 mg/25 mg Film-coated Tablets contain the cardioselective β-blocker atenolol and may, therefore, be used with caution in patients with obstructive airways disease. If increased airways resistance develops consideration must be given to discontinuation of the β-blocker, depending on the degree of airways resistance and the benefit derived from β-blockade.

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. Measurement of potassium levels is appropriate in all patients, especially older patients, who may be receiving digitalis preparations for cardiac failure, taking abnormal (low in potassium) diets, or suffering from gastrointestinal complaints.

Tenoretic 100 mg/25 mg Film-coated Tablets are generally associated with only a minor increase in serum uric acid. In cases of prolonged elevation the concurrent use of uricosuric agents will reverse the hyperuricaemia. Hyperuricaemia or acute gout may occur.

Tenoretic 100 mg/25 mg Film-coated Tablets contain chlortalidone which may decrease glucose tolerance. During prolonged therapy regular tests for glycosuria should be carried out. Care is necessary when Tenoretic 100 mg/25 mg Film-coated Tablets are administered to patients with a known predisposition to diabetes.

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

Tenoretic 100 mg/25 mg Film-coated Tablets 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.

Tenoretic 100 mg/25 mg Film-coated Tablets modifies the tachycardia of hypoglycaemia.

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.

Because Tenoretic 100 mg/25 mg Film-coated Tablets contains chlortalidone, care should be taken in patients with severe renal failure.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

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

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.

Preparations containing lithium generally should not be given with diuretics because they may reduce its renal clearance.

Tenoretic 100 mg/25 mg Film-coated Tablets should only be used with great caution in patients who are receiving concomitant myocardial depressants such as chloroform, ether or related anaesthetics, anti-arrhythmic agents such as quinidine, lignocaine, procainamide (which accentuate depressant effects), beta-adrenoceptor stimulants such as isoprenaline or alpha-adrenoceptor stimulants such as noradrenaline (norepinephrine), adrenaline (epinephrine) (which reverse the antihypertensive effects and increase the vasoconstrictor activities).

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.

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

Potassium depletion may be dangerous in patients receiving digitalis.

Concomitant use of sympathomimetic agents, e.g. adrenaline, (epinephrine), may counteract the effect of beta-blockers.

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

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

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.

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

The use of Tenoretic 100 mg/25 mg Film-coated Tablets 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 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 (10%), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0-09%), very rare (<0.01%):

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.

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 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.

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

Beta-blocking agents, selective and other diuretics 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 beta1 -selective (i.e. acts preferentially on beta1 -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 beta2-effects. In addition, and in contrast to the non-selective agents, atenolol preserves the beta2-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 50mg 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 300ng/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 950ng/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

Heavy magnesium carbonate
Maize starch
Sodium laurilsulfate
Gelatin
Magnesium stearate
Hypromellose
Macrogol 300
Iron oxide (E172)
Magnesium carbonate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.
Keep the blister in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/aluminium foil blister strips in an over-labelled cardboard carton containing 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2009

10 DATE OF REVISION OF THE TEXT

September 2011