IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1500/016/001
Case No: 2083742

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Profind Wholesale Ltd.

Unit 625, Kilshane Avenue, **Northwest Business Park**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Tenoret 50 mg/12.5 mg Film-coated Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/07/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tenoret 50 mg/12.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains atenolol 50 mg and chlortalidone 12.5 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Product imported from the UK:
Brown, biconvex, film-coated tablet imprinted with the name Tenoret 50 on one face and an ‘S’ logo on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The management of hypertension after initial stabilisation has been achieved with the active ingredients used separately.

4.2 Posology and method of administration

Adults
One tablet daily.

Patients with hypertension who do not respond to low dose therapy with a single agent or where full doses of both may be considered inappropriate, should have a satisfactory response to a single tablet daily of Tenoret 50 mg/12.5 mg Film-coated Tablets. Where hypertensive control is not achieved, addition of a small dose of a third agent, e.g. a vasodilator, may be appropriate.

Children
There is no paediatric experience with Tenoret 50 mg/12.5 mg Film-coated Tablets, and for this reason it is not recommended for children.

Renal Failure
Caution should be exercised in patients with severe renal failure. The dose should be reduced by decreasing the frequency of administration (see section 4.4).

4.3 Contraindications

Tenoret 50mg/12.5mg film-coated tablets should not be used in patients with any of the following: known hypersensitivity to either component; 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 and in digitalis intoxication.

Tenoret 50mg/12.5mg 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 50mg/12.5mg film-coated tablets:

- Although contra-indicated 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 Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Atenolol is a $beta_1$- selective beta-blocker; consequently the use of Tenoret 50mg/12.5mg film-coated tablets may be considered although utmost caution must be exercised.

- Although contraindicated in severe peripheral arterial circulatory disturbances (see Contra-indications), 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 tachycardia of hypoglycaemia.

- May mask the 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.

- May cause an increase in airways resistance. Tenoret 50mg/12.5mg film-coated tablets can be administered with caution in patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the drug, depending on the degree of airways resistance and the benefit derived from ß-blockade. The beta blocker should only be used with caution in patients with a family history of asthma.

Due to its chlortalidone component:

- Hypokalaemia may occur. Regular supervision and measurement of potassium levels is appropriate, especially in the older patient, those receiving digitalis preparation 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).

- Impaired glucose tolerance may occur and caution must be exercised if chlortalidone is administered to patients with a known predisposition to diabetes mellitus.

- 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 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 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.

Concomitant therapy with dihydropyridines, e.g. 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.

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.

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 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.

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

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.

Adjustment of the dosage of hypoglycaemic agents may be necessary if given with uncontrolled or “brittle” diabetes mellitus.

4.6 Pregnancy and lactation

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

Lactation
Tenoret 50 mg/12.5 mg Film-coated 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

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 (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.

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 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.

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

Beta-blocking agents, selective and other diuretics 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 beta1- 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 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

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

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.
PVC/Aluminium foil blister strips (box of 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 1500/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28th May 2009

10 DATE OF REVISION OF THE TEXT

July 2010