Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tenormin 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100mg atenolol.

Excipients:
Product imported from the UK – Sunset Yellow (E110)

For full list of excipients, *see section 6.1*.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from The UK:
Round, bi-convex, orange tablets with 'TENORMIN' on one side and a 'Z' symbol on the other.

Product imported from the Netherlands:
Round, bi-convex, white tablets with 'TENORMIN 100' on one side and a breakline on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Control of hypertension;
Management of angina pectoris;
Control of cardiac arrhythmias;
In early intervention in the acute phase of myocardial infarction and long-term prophylaxis after recovery from myocardial infarction.

4.2 Posology and method of administration

Adults:

Control of Hypertension: Most patients respond to 50 mg daily given as a single dose. Some patients may respond to 100 mg given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining 'Tenormin' with other antihypertensive agents.

Management of Angina Pectoris: Most patients with angina pectoris will respond to 100 mg once daily or 50 mg twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Control of cardiac Arrhythmias: An oral maintenance dose of Tenormin is 50-100 mg daily, given once daily.

Early and late intervention after Myocardial infarction:
Early and late intravention after Myocardial Infarction: Oral treatment with Tenormin can be initiated in haemodynamically stable patients with 50 mg twice daily, and then 100 mg once daily. During the early phase of acute myocardial infarction, treatment with Tenormin should be initiated in hospital under close monitoring. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, Tenormin should be discontinued.

Tenormin100 mg daily is recommended for long-term prophylaxis of myocardial infarction.

Children: there is no paediatric experience with 'Tenormin' and for this reason it is not recommended for use in children.

Elderly: Dosage requirements may be reduced, especially in patients with impaired renal function.

Renal Failure: Since Tenormin is excreated via the kidneys dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of Tenormin occurs in patients who have a creatine clearance greater than 35ml/min/1.73m^2 (normal range is 100-150ml/min/1.73m^2). For patients with a creatine clearance of 15-35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300-600 micromol/litre) the dose should be 50mg daily. For patients with a creatinine clearance of less than 15ml/min/1.73 m^2 (equivalent to serum creatinine of >600 micromol/litre) the dose should be 25mg daily or 50mg on alternate days. Patients on haemodialysis should be given 50mg orally after each dialysis: this should be done under hospital supervision as marked falls in blood pressure can occur.

4.3 Contraindications

'Tenormin' as with other beta-blockers should not be used in patients with any of the following: known hypersensitivity to the active substance or any of the excipients; 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.

4.4 Special warnings and precautions for use

'Tenormin' as with other beta-blockers:

- Should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7-14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.
- When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk –benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.
- 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 used in patients whose cardiac reserve is poor.
- May increase the number and duration of angina attacks in patients with Prinzmental's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. 'Tenormin' is a beta$_1$-selective beta-clocker; consequently, its use may be considered although utmost caution must be exercised.
- Although contra-indicated in severe peripheral arterial circulatory disturbances *(see section 4.3)* may also aggravate less severe peripheral arterial circulatory disturbances.
- Due to it snegative 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, and the pulse rate drops to less than 50-55 bpm at rest, the dose may be reduced.
- 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 is asthmatic patients. 'Tenormin' is a beta^1-selective beta-blocker;

consequently its use may be considered although utmost caution must be exercised. If increased airways resistance does occur, 'Tenormin' should be discontinued and bronchodilator therapy (eg salbutamol) administered if necessary.

- Should only be given to patients with psoriasis after careful consideration, as psoriasis may be aggravated.

Since Tenormin is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35ml/min/1.73m².

As with other beta-blockers, in patients with a phaeochromcytoma, an alpha-blocker should be given concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

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

Anaestheic agents
Caution must be exercised when using anaesthetic agents with tenormin. 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.

Antiarrhythmic agent (Class 1)
Caution must be exercised when prescribing a beta-blocker with Class 1 antiarrhythmic agents such as disopyramide.

Calcium channel blockers
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 sinoatrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blockers nor the calcium channel blockers should be administered intravenously within 48 hours of discontinuing the other.

Clonidine
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 (see also prescribing information for clonidine).

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

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

Insulin and oral antidiabetic drugs
Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked *(See section 4.4).*

Myocardial depressants
The beta-blockers should only be used with caution in patients who are receiving concomitant myocardial depressants such as halogenated anaesthetics, lidocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline (norepinephrine).

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

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

4.6 Fertility, pregnancy and lactation

'Tenormin' crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of 'Tenormin' in the first trimester and the possibility of foetal injury cannot be excluded. 'Tenormin' has been used under close supervision for the treatment of hypertension in the third trimester. Administration of 'Tenormin' to pregnant women in the management of mild to moderate hypertension has been associated with the intra-uterine growth retardation. The use of 'Tenormin' in women who are, or may become pregnant requires that the anticipated benefit be weighted against the possible risks, particularly in the first and second trimesters.

There is significant accumulation of 'Tenormin' in breast milk.
Neonates born to mothers who are receiving Tenormin at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. Caution should be exercised when 'Tenormin' is administered during pregnancy or to women who is breast-feeding.

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

'Tenormin' is well tolerated. In clinical trial studies, the undesired events reported are usually attributable to the pharmacological actions of atenolol.

The following undesired events, 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%) including isolated reports.

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.

Nervous system disorders:
Rare: Dizziness, headache, paraesthesia.

Psychiatric disorders:
Uncommon: Sleep disturbances of the type noted with other beta-blockers.
Rare: Mood changes, nighmares, confusion, psychoses and hallucinations.

Gastrointestinal disorders;
Common: Gastrointestinal disturbances.
Rare: Dry mouth.

Investigations:

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.

Hepato-biliary disorders:
Rare: Hepatic toxicity including intrahepatic cholestasis.

Blood and lymphatic system disorders:
Rare: Purpura, thrombocytopenia.

Skin and subcutaneous tissue disorders:
Rare: Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Eye disorders:
Rare: Dry eyes, visual disturbances.

Reproductive system and breast disorders;
Rare: Impotence

Respiratory, thoracic and mediastinal disorders;
Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

General disorders and administration site conditions:
Common: Fatigue

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patients 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 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 uses of haemodialysis or haemoperfusion may be considered.

Excessive bardycardia can be countered with atropine 1-2mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Betablocking agents, selective
ATC Code: CO7A BO3

Atenolol is a beta-blocker which 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 contra-indicated in uncontrolled heart failure)

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

It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

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.
'Tenormin' is effective and well-tolerated in most ethnic populations although the response may be less in black patients.

'Tenormin' is compatible with diuretics, other antihypertensive agents and antianginal agents *(see section 4.5).*

5.2 Pharmacokinetic properties

Following intravenous administration, the blood levels of atenolol decay tri-expotentially with an elimination half-life of about 6 hours. Throughout the intravenous dose range of 5-10mg the blood level profile obeys linear pharmacokinetics and beta-blockade is still measurable 24 hours after a 10mg intravenous dose.

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%).

'Tenormin' is 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 is a drug 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

Excipients present in the tablets imported from The UK:

Gelatin
Magnesium carbonate (E504)
Magnesium stearate (E572)

Hypromellose (E464)
Sodium laurilsulfate
Maize starch
Titanium dioxide (E171)
Macrogol
Sunset yellow lake (E110)
Talc (E553 (b))

Excipients present in the tablets imported from the Netherlands:

Magnesium carbonate (E504)
Maize starch
Sodium laurilsulfate
Gelatin
Magnesium stearate (E572)
Hypromellose (E464)
Glycerol (E422)
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of these products is the date shown on the container and outer package of the products on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C
Store in the original package.

6.5 Nature and contents of container

Blister packs containing 28 or 30 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

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/023/002.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 January 1991

Date of last renewal: 14 January 2006

10 DATE OF REVISION OF THE TEXT

April 2011