

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

'Tenormin' Injection 0.5mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol 0.5mg/ml (5mg in 10ml)

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Ampoules containing a clear, colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of cardiac arrhythmias and in early intervention after myocardial infarction.

4.2 Posology and method of administration

Adults:

Arrhythmias: A suitable initial dose of 'Tenormin' is 2.5mg (5ml) injected intravenously over a 2.5 minute period (i.e. 1mg/minute). This may be repeated at 5 minute intervals until a response is observed up to a maximum dosage of 10mg. If 'Tenormin' is given by infusion, 0.15mg/kg bodyweight may be administered over a 20-minute period. If required, the injection or infusion may be repeated every 12 hours. Having controlled the arrhythmias with intravenous 'Tenormin', a suitable oral maintenance dosage is 50-100mg daily, given as a single dose.

Early Intervention After Acute Myocardial Infarction: Reduction of infarct size, incidence of ventricular arrhythmias, morbidity, pain, need for opiate analgesics and early mortality: For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of chest pain, 'Tenormin' 5-10mg should be given immediately by slow intravenous injection (1mg/minute) followed by 'Tenormin' 50mg orally about 15 minutes later provided no untoward effects occur from the intravenous dose.

This should be followed by 50mg orally 12 hours after the intravenous dose and then 12 hours later by 100mg orally to be given once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, 'Tenormin' should be discontinued.

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 excreted 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 creatinine clearance greater

than 35ml/min/1.73m² (normal range is 100-150 ml/min/1.73m²). For patients with a creatinine clearance of 15-35ml/min/1.73m² (equivalent to serum creatinine of 300-600 micromol/litre) the intravenous dose should be 10mg once every two days. For patients with a creatinine clearance of <15ml/min/1.73m² (equivalent to serum creatinine of > 600 micromol/litre) the intravenous dose should be 10mg every four 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 special precautions for use

'Tenormin' as with other beta-blockers:

- 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.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. 'Tenormin' is a beta₁-selective beta-blocker; 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 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.
- 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 an increase in airways resistance in asthmatic patients. 'Tenormin' is a beta₁-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 (e.g. salbutamol) administered if necessary.
- Tenormin injection is compatible with sodium chloride intravenous infusion (0.9% w/v) and glucose Intravenous Infusion BP (5% w/v).

4.5 Interaction with other medicinal products and other forms of interaction

The betablocker should only be used with caution in patients who are receiving concomitant myocardial depressants

such as halogenated anaesthetics, lignocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline.

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

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 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.

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

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

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

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.

4.6 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 weighed 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. Caution should be exercised when 'Tenormin' is administered during pregnancy or to a woman 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 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.

Cardiovascular: bradycardia; heart failure deterioration; postural hypotension which may be associated with syncope; cold extremities. In susceptible patients: precipitation of heart block; intermittent claudication, Raynaud's phenomenon.

CNS: confusion; dizziness; headache; mood changes; nightmares; psychoses and hallucinations; sleep disturbances of the type noted with other beta-blockers.

Gastrointestinal: dry mouth, gastrointestinal disturbances, elevations of transaminase levels have been seen infrequently, rare cases of hepatic toxicity including intrahepatic cholestasis have been reported.

Haematological: purpura; thrombocytopenia

Integumentary: alopecia; dry eyes; psoriasiform skin reactions; exacerbation of psoriasis; skin rashes.

Neurological: paraesthesia.

Reproductive: impotence.

Respiratory: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Special senses: Visual disturbances.

Others: fatigue; an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

Discontinuance of the drug 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 uses of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia 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

CO7A BO3

Atenolol is a beta-blocker which is beta₁-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 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-exponentially 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

Anhydrous Citric Acid.
Sodium Chloride
Sodium Hydroxide
Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Keep the container in the outer carton.

For single use only. Once opened, any unused solution should be discarded.

6.5 Nature and contents of container

Type I clear glass ampoules (10 x 10ml ampoules).

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd.,
600 Capability Green,
Luton, LU1 3LU,
UK

8 MARKETING AUTHORISATION NUMBER

PA 970/19/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th May 1982

Date of last renewal: 18th May 2002

10 DATE OF REVISION OF THE TEXT

April 2005