Tenormin

Atenolol

Film-coated tablets 50mg, 100mg

Composition

Tablets containing 50 mg or 100 mg of Atenolol Ph. Eur.

For excipients see *List of excipients.*

Therapeutic Indications

i) Hypertension.
ii) Angina pectoris.

Posology and method of administration

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines.

Adults

Hypertension
One tablet daily. Most patients respond to 100 mg daily given orally as a single dose. Some patients, however, will respond to 50 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.

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

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

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

Renal Failure
Since Tenormin is excreted via the kidneys the dosage should be reduced in cases of severe impairment of renal function.

No significant accumulation of Tenormin occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2).

For patients with a creatinine clearance of 15-35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300-600 micromol/litre) the oral dose should be 50 mg daily and the intravenous dose should be 10 mg once every two days.

For patients with a creatinine clearance of <15 ml/min/1.73 m^2 (equivalent to serum creatinine of >600 micromol/litre) the oral dose should be 25 mg daily or 50 mg on alternate days and the intravenous dose should be 10 mg once every four days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

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 (<45bpm); cardiogenic shock; hypotension; metabolic acidosis; severe peripheral arterial circulatory disturbances; second or third degree heart block; sick sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure.

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 contraindicated in uncontrolled heart failure (see *Contraindications*), 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 $beta_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.

- although contraindicated in severe peripheral arterial circulatory disturbances (see *Contraindications*), 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 mask the symptoms of hypoglycaemia, in particular, tachycardia.

- 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 50-55bpm at rest, the dose should 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 used to treat the allergic reactions.

- may cause a hypersensitivity reaction including angioedema and urticaria

- should be used with caution in the elderly, starting with a lesser dose (see *Posology and method of administration*).

Since Tenormin is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35ml/min/1.7m^2.

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, Tenormin 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.

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

Interactions

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 atrio-ventricular 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. (See also prescribing information for clonidine).

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents, e.g. adrenaline, 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. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see *Special warnings and precautions for use*).

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.

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 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, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

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 a woman who is breast-feeding.

Effect 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.

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: hypersensitivity reactions, including angioedema and urticaria; 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.

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 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-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.

Pharmacodynamic properties

Betablocking agents, plain selective, CO7A B03

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 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 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 effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Tenormin is compatible with diuretics, other hypotensive agents and antianginal agents (see *Interactions*). Since it acts preferentially on beta-receptors in the heart, Tenormin may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

Early intervention with Tenormin in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Tenormin is an additional treatment to standard coronary care.

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 5-10 mg the blood level profile obeys linear pharmacokinetics and beta-adrenoceptor blockade is still measurable 24 hours after a 10 mg 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%).

List of excipients

Tablets: Gelatin, Glycerol, Magnesium carbonate, Magnesiun stearate, Maize starch, Hypromellose, Sodium lauryl sulphate, Titanium hydroxide.
100 mg tablets only: Macrogol 300, Sunset yellow lake.

Shelf-life

Please refer to expiry date on the blister strip or outer carton.

Special precautions for storage

Tenormin Tablets: Do not store above 25°C. Protect from light and moisture.

Pack Size
Please refer to the outer carton for pack size.

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