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TENORETIC
ASTRAZENECA

Atenolol/chlorthalidone
Tablets

Composition
Tablets containing 100 mg of Atenolol Ph. Eur. and 25 mg of Chlorthalidone Ph.Eur.

Pharmaceutical form
White, round, biconvex, film coated tablets

Therapeutic Indications
Hypertension.

Posology and method of administration
Adults
One tablet daily. Most patients with hypertension will give a satisfactory response to a single tablet daily of Tenoretic. There is little or no further fall in blood pressure with increased dosage but, where necessary, another antihypertensive drug, such as a vasodilator, can be added.

Elderly
Dosage requirements are often lower in this age group.

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

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

Contra-indications
Tenoretic 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.

Tenoretic must not be given during pregnancy or lactation.

Special warnings and precautions for use
Due to its beta-blocker component Tenoretic:

- although contra-indicated in uncontrolled heart failure (see Contra-indications), 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. Atenolol is a beta-1 selective beta-blocker; consequently the use of Tenoretic may be considered although utmost caution must be exercised.
- although contra-indicated 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.
- 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. Atenolol is a beta1-selective beta blocker; consequently the use of Tenoretic may be considered although utmost caution must be exercised. If increased airways resistance does occur,

Tenoretic should be discontinued and bronchodilator therapy (eg salbutamol) administered if necessary.

Due to its chlorthalidone component:

- hypokalaemia may occur. Measurement of potassium levels is appropriate, especially in the older patient, those receiving digitalis preparations 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 Dosage and administration).
- impaired glucose tolerance may occur and caution must be exercised if chlorthalidone is administered to patients with a known pre-disposition to diabetes mellitus.
- hyperuricaemia 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.

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 eg. 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, eg adrenaline, may counteract the effect of beta-blockers.

Concomitant use of prostaglandin synthetase inhibiting drugs (eg. ibuprofen, indomethacin) 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 Tenoretic. 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

Pregnancy: Tenoretic must not be given during pregnancy.

Lactation: Tenoretic must not be given during lactation.

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

Tenoretic is well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of its components.

The following undesired events, listed by body system, have been reported with Tenoretic or either of its components:

Biochemical: hyperuricaemia, hyponatraemia (related to chlorthalidone), hypokalaemia, impaired glucose tolerance (see Warnings/precautions).

Cardiovascular: bradycardia; heart failure deterioration; postural hypotension which may be associated with syncope; cold extremities. In susceptible patients: precipitation of heart block; intermittent claudication may be increased if already present; 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; nausea (related to chlorthalidone), pancreatitis.
Haematological: leucopenia; purpura; thrombocytopenia.
Integumentary: alopecia; dry eyes; psoriasiform skin reactions; exacerbation of psoriasis; skin rashes.
Neurological: paraesthesia.
Respiratory: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.
Reproductive: impotence
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 Tenoretic 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 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.

Pharmacodynamic properties

Tenoretic combines the antihypertensive activity of two agents, a beta-blocker (atenolol) and a diuretic (chlorthalidone).

Atenolol is beta-1 selective (ie 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 unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Chlorthalidone, a monosulfonamyl diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by which chlorthalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium.

Atenolol is effective and well-tolerated in most ethnic populations. Black patients respond better to the combination of atenolol and chlorthalidone, 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.

Pharmacokinetic properties

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%).

Absorption of chlorthalidone following oral dosing is consistent but incomplete (approximately 60%) with peak plasma concentrations occurring about 12 hours after dosing. The chlorthalidone 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 chlorthalidone and atenolol has little effect on the pharmacokinetics of either.

Tenoretic is effective for at least 24 hours after a single oral daily dose. This simplicity of dosing facilitates compliance by its acceptability to patients.

Excipients

Maize starch, heavy magnesium carbonate, gelatine, sodium lauryl sulphate, magnesium stearate, hypromellose, glycerol, and titanium dioxide.

Storage

Do not store above 25oC. Protect from light and moisture.

Shelf life

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

Pack Size

Please refer to the outer carton for pack size.

Date of revision of the text

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