Blokium DIU™

(Atenolol + Chlorthalidone)

Highnoon

COMPOSITION

Blokium DIU 50 Tablet: Each tablet contains: Atenolol 50mg Chlorthalidone 12.5mg

Blokium DIU 100 Tablet: Each tablet contains: Atenolol 100mg Chlorthalidone 25mg

DESCRIPTION

Blokium DIU is a combination of Atenolol is a synthetic, beta,-selective (cardio selective) adrenoreceptor blocking agent, without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities and Chlorthalidone a monosulfonamyl diuretic.

MECHANISM OF ACTION

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 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. Chlorthalidone exerts its therapeutic action by antagonizing sodium-chloride symporter in the distal convoluted tubule of the nephron. It is similar to a thiazide diuretic in its mechanism of action, although it has a mildly altered chemical structure. Chlorthalidone inhibits sodium reabsorption at the level of the distal convoluted tubule and thus chloride via inhibition of the Na/Cl symporter. By removing sodium reabsorption at this location, the distal convoluted tubule of the nephron retains a higher sodium content. This lack of reabsorption alters the osmotic gradient and shifts fluid distribution from the outside of the tubule to the inside of the tubule. The increased osmotic load from its increased sodium concentration leads to elevated intratubular volume, thus promoting its diuretic effect. The increased excretion of sodium and extracellular fluid decreases intravascular water and solute concentration. By lowering the intravascular volume and osmotic gradient, the patient has reduced hydrostatic pressure leading to a clinical reduction in blood pressure.

PHARMACOKINETICS

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The bioavailability is decreased by 20% when taken with food. There is a linear relationship between dosage and plasma concentration. The inter-subject variability in AUC and Cmax is about 30-40%. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. The volume of distribution is 50 to 75 L. The protein binding is low (approximately 3%). Most of an absorbed dose (85-100%) is excreted unchanged via the urine. The clearance is about 6 l/h and the half-life is about 6 to 9 hours. In elderly patients, clearance is decreased and elimination half-life increased. The clearance is correlated to renal function and the elimination is prolonged in patients with renal impairment. Impaired liver function does not influence the pharmacokinetics of atenolol. Chlorthalidone is an oral diuretic with prolonged action and low toxicity. 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%). Coadministration of chlortalidone and atenolol has little effect on the pharmacokinetics of either. tAtenolol and Chlorthalidone combination is effective for at least 24 hours after a single oral daily dose.

INDICATION

Atenolol and Chlorthalidone combination is for the management of hypertension.

DOSAGE AND ADMINISTRATION

Blokium DIU 50 and Blokium DIU 100 are for oral administration only.

Adults

One tablet daily.

Elderly

One tablet daily. The elderly with hypertension who do not respond to low dose therapy with a single agent should have a satisfactory response to a single tablet daily of Atenolol and Chlorthalidone combination. Where hypertensive control is not achieved, addition of a small dose of a third agent e.g. as a vasodilator, may be appropriate.

Paediatric Population

The use of Atenolol and Chlorthalidone combination is not recommended in children. The safety and efficacy of Blokium DIU in children has not yet been established.

Renal Impairment

Due to the properties of the chlortalidone component, Atenolol and Chlorthalidone combination has reduced efficacy in the presence of renal insufficiency. This fixed dose combination should thus not be administrated to patients with severe renal impairment.

CONTRAINDICATIONS

Atenolol should not be used in patients with any of the following:

- hypersensitivity to the active substance, or to any of the excipients
- cardiogenic shock
- uncontrolled heart failure
- sick sinus syndrome
- second-or third-degree heart block
- untreated phaeochromocytoma
- metabolic acidosis
- bradycardia (<45 bpm)
- hypotension
- severe peripheral arterial circulatory disturbances.
- Renal failure
- Not to be given in pregnancy and lactation.

WARNINGS AND PRECAUTIONS

Atenolol, 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.
- For scheduled surgery and discontinuation of beta-blocker therapy, decision should be made 24 before the procedure after weighing risk and benefit. 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 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 beta1-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances, 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 50–55 bpm 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 (epinephrine) 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.
- Since atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m².
- Although cardioselective (beta1) 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, atenolol 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.
- If patient with history of asthma or wheezing requires atenolol, consultation with the doctor is advised.
- Impaired glucose tolerance may occur and diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy test for glucosuria should be carried out at regular intervals.
- Plasma electrolyte should be periodically determined in appropriate intervals to detect possible electrolyte imbalance especially hypokalaemia and hyponatraemia.
- Hypokalaemia and hyponatraemia may occur. Measurement of electrolytes is recommended, 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.
- 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.
- Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
- In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma.
- Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

ADVERSE EFFECTS

The following have been reported with the use of atenolol:

purpura, thrombocytopenia, sleep disturbances of the type noted with other beta-blockers, mood changes, nightmares, confusion, psychoses and hallucinations, dizziness, headache, paraesthesia, dry eyes, visual disturbances, bradycardia, heart failure deterioration, precipitation of heart block, cold extremities, postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, gastrointestinal disturbances, dry mouth, elevations of transaminase levels, hepatic toxicity including intrahepatic cholestasis, alopecia, psoriasis, exacerbation of psoriasis, skin rashes, hypersensitivity reactions, including angioedema and urticaria Lupus-like syndrome, impotence, fatigue, an increase in ANA (Antinuclear Antibodies) has been observed, leucopenia, choroidal effusion, hepatic toxicity including intrahepatic cholestasis, pancreatitis, hyperuricaemia, hyponatraemia, hypokalaemia and impaired glucose tolerance

The reported adverse effects of chlorthalidone are: decrease appetite, dizziness, electrolyte imbalance (including) dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps, seizures, oliguria, and hypotension), erectile dysfunction, gastrointestinal discomfort, hyperglycemia, hyperuricemia, skin reactions, gout, agranulocytosis, alkalosis, hyperchloremic, arrhythmia, diabetes mellitus exacerbated, diarrhea, eosinophilia, glycosuria, hepatic disorder, nausea, nephritis tubulo interstitial, pancreatitis, paresthesia, photosensitivity reactions, pulmonary oedema, respiratory disorder, vomiting, anorexia, constipation, sialadenitis, yellow vision, impotence, hypersensitivity reactions (including rashes, fever, pulmonary edema, pneumonitis, anaphylaxis, and epidermal necrolysis), cancer, blood dyscrasia, including thrombocytopenia, granulocytopenia, leukopenia, aplastic and hemolytic anemia.

DRUG INTERACTIONS

- Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g., verapamil and diltiazem, can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sinoatrial 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. (See also prescribing information for clonidine.)
- 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 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.
- Concomitant use of prostaglandin synthetase-inhibiting drugs, e.g. ibuprofen and indomethacin, may decrease the hypotensive effects of beta-blockers.
- Caution must be exercised when using anaesthetic agents with atenolol. 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.
- The chlortalidone component may reduce the renal clearance of lithium leading to increased serum concentrations. Dose adjustments of lithium may therefore be necessary.
- Concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.
- Concomitant use of baclofen may increase the antihypertensive effect making dose adjustments necessary.

USE IN SPECIFIC POPULATIONS

PREGNANCY AND LACTATION

Not to be given during pregnancy and lactation. There is no data available on fertility.

OVERDOSAGE

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 1–2 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. Excessive diuresis should be countered by maintaining normal fluid and electrolyte balance.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION

Blokium DIU 50 Tablets: Alu. PVC. Blister Pack of 2 x10's.

Blokium DIU 100 Tablets: Alu. PVC. Blister Pack of 2 x10's.

بلوکیم ڈی آئی یو™

(ایٹی نولول + کلورتھیلیڈون)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔

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