

Cardiolite Plus

(Atenolol + Chlorthalidone)

کارڈیولائٹ پلس

COMPOSITION

Each **Cardiolite Plus** film coated tablet contains 50mg of atenolol and 12.5mg of chlorthalidone.

MECHANISM OF ACTION

Cardiolite Plus combines the antihypertensive activity of two agents: a beta1-selective (cardioselective) hydrophilic blocking agent (atenolol) and a diuretic (chlorthalidone).

Cardiolite Plus may be administered with other antihypertensives such as vasodilators.

Atenolol

Atenolol is a beta1-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery and (3) suppression of renin activity.

Chlorthalidone

Chlorthalidone, a monosulfonamyl diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron. The mechanism by which chlorthalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium.

PHARMACOKINETICS

Atenolol

Absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 and 4 hours after ingestion. Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Only a small amount (6 - 16%) is bound to proteins in the plasma. The elimination half-life of atenolol is approximately 6 to 7 hours. Following doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; but significant accumulation does not occur until the creatinine clearance falls below 35 mL/min/1.73m².

Chlorthalidone

After an oral dose about 65% is absorbed. Peak serum levels are reached 2-6 hours after administration. The diuretic effect of the drug occurs within 2 hours of an oral dose. The plasma half-life is 50-90 hours. During long term treatment 30-60% of the dose is excreted unchanged in the urine and up to 10% excreted in the feces. No metabolites have been identified.

Cardiolite Plus tablet is effective for at least 24 hours after a single oral daily dose.

INDICATIONS

Cardiolite Plus is indicated in the treatment of hypertension. This fixed dose combination drug is not indicated for initial therapy of hypertension. If the fixed dose combination represents the dose appropriate to the individual patient's need, it may be more convenient than the separate components.

DOSAGE AND ADMINISTRATION

One **Cardiolite Plus** tablet once a day.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function.

UNDESIRABLE EFFECTS

In clinical studies, the possible adverse reactions are usually attributable to the pharmacological actions of its components. The following undesirable effects, 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%), not known (cannot be estimated from available data):

Blood and lymphatic system disorders:

Rare: Purpura, thrombocytopenia, neutropenia, leucopenia (related to chlorthalidone).

Psychiatric disorders:

Uncommon: Sleep disturbances noted with other beta-blockers.

Rare: Mood changes, nightmares, confusion, psychoses and hallucinations.

Nervous system disorders:

Rare: Dizziness, headache, paraesthesia.

Eye disorders:

Rare: Dry eyes, visual disturbances.

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.

Respiratory, thoracic and mediastinal disorders:

Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Gastrointestinal disorders:

Common: Gastrointestinal disturbances (including nausea related to chlorthalidone).

Rare: Dry mouth.

Not known: Constipation.

Hepatobiliary disorders:

Rare: Hepatic toxicity including intrahepatic cholestasis, pancreatitis (related to chlorthalidone).

Skin and subcutaneous tissue disorders:

Rare: Alopecia, psoriasiform skin reaction, exacerbation of psoriasis, skin rashes.

Musculoskeletal and connective tissue disorders:

Not known: Muscle fatigue.

Reproductive system and breast disorders:

Rare: Impotence.

General disorders:

Common: Fatigue.

Investigations:

Common (related to chlorthalidone): Hyperuricaemia, hyponatraemia, hypokalaemia, impaired glucose tolerance.

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.

Discontinuation should be considered if, according to clinical judgment, the well-being of the patient is adversely affected by any of the above reactions. Discontinuation of therapy with a beta-blocker should be gradual.

DRUG INTERACTIONS

- **Cardiolite Plus** may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with **Cardiolite Plus** plus a catecholamine depletor (eg, reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.
- Calcium channel blockers may also have an additive effect when given with **Cardiolite Plus**.
- Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect. Disopyramide is a Type I antiarrhythmic drug with potent negative inotropic and chronotropic effects.
- Disopyramide has been associated with severe bradycardia, asystole and heart failure when administered with beta blockers. Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with beta blockers.
- Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.
- Concomitant use of prostaglandin synthase inhibiting drugs, eg, indomethacin, may decrease the hypotensive effects of beta blockers.
- Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity.
- Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs

are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

- While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.
- Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

PRECAUTIONS

General

Cardiolite Plus may aggravate peripheral arterial circulatory disorders.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

Electrolyte and Fluid Balance Status

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Patients should be observed for clinical signs of fluid or electrolyte imbalance; i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Use in Pregnancy

Pregnancy Category D.

Nursing Mothers

Atenolol is excreted in human breast milk. Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

WARNINGS

Cardiac Failure

In patients who have congestive heart failure controlled by digitalis and/or diuretics, **Cardiolite Plus** should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, **Cardiolite Plus** should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances

Since atenolol is excreted via the kidneys, **Cardiolite Plus** should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, **Cardiolite Plus** should be discontinued. In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. **Cardiolite Plus** should be used with caution in these patients.

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported.

Concomitant Use of Calcium Channel Blockers

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with preexisting conduction abnormalities or left ventricular dysfunction are particularly susceptible.

Bronchospastic Disease

Patients with bronchospastic disease should, in general, not receive beta blockers. Because of its relative beta1-selectivity, however, **Cardiolite Plus** may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate other antihypertensive treatment. Since beta1-selectivity is not absolute, the lowest possible dose of **Cardiolite Plus** should be used and a beta2-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery

It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV). Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution.

Metabolic and Endocrine Effects

Cardiolite Plus may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels. Insulin requirements in diabetic patients may be increased, decreased or unchanged; latent diabetes mellitus may become manifest during chlorthalidone administration. Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom **Cardiolite Plus** therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, **Cardiolite Plus** should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Hyperuricemia may occur, or acute gout may be precipitated in certain patients receiving thiazide therapy.

Untreated Pheochromocytoma

Cardiolite Plus should not be given to patients with untreated pheochromocytoma.

OVERDOSE

Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.

CONTRAINDICATIONS

Cardiolite Plus is contraindicated in patients with:

Sinus bradycardia; heart block greater than first degree; cardiogenic shock; overt cardiac failure; anuria; hypersensitivity to this product or to sulfonamide-derived drugs.

PRESENTATION

Cardiolite Plus Tablet: 3x10's/pack.

Dosage:

As directed by the physician.

Instructions:

Store below 30°C.

Protect from sunlight & moisture.

Keep out of reach of children.

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Detailed prescribing information is available on request.

خوراک:

ڈاکٹر کی ہدایت کے مطابق۔

ہدایات:

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔