Herbesser®

(Diltiazem HCl)

Highnoon

COMPOSITION
Herbesser 30 Tablet:
Each tablet contains: Diltiazem HCl 30mg
Herbesser 60 Tablet:
Each tablet contains: Diltiazem HCl 60mg

DESCRIPTION
Diltiazem HCl is a calcium ion cellular influx inhibitor. The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the cellular influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

MECHANISMS OF ACTION
Diltiazem hydrochloride dilates blood vessels, improves myocardial ischaemia, and exerts antihypertensive effects by inhibiting calcium channel influx to cells in vascular smooth muscles such as coronary vessels, peripheral vessels, etc.
Action on myocardial ischaemia:
Improvement of myocardial oxygen demand and supply balance: It dilates large coronary vessels and collateral channels and increases blood flow to myocardial ischaemic lesions. It inhibits coronary artery spasm. It decreases myocardial oxygen consumption by afterload reduction due to peripheral vasodilation and decreased heart rate without decreasing cardiac output.
Myocardial protective action: It maintains cardiac function and myocardial energy metabolism and reduces the extension of infarct lesions by inhibiting calcium channel influx to cells at the time of myocardial ischaemia.
Action on blood pressure:
It has almost no effect on normal blood pressure, while decreases high blood pressure gradually and inhibits exercise-induced blood pressure elevation.
It does not decrease cerebral and renal blood flow, while decreases blood pressure. It inhibits myocardial and vascular hypertrophies along with decreased blood pressure. Effects on cardiac stimulation and cardiac conduction It slightly prolongs sinus node spontaneous cycle length and slows atrioventricular nodal conduction (AH interval), while it does not affect His-Purkinje system conduction.

PHARMACOKINETICS
Plasma concentration of this product after oral administration of two tablets of HERBESSER Tablets 30 (60 mg of diltiazem hydrochloride) to healthy male adults reached maximum at 3 to 5 hours after the administration, and thereafter decreased with an elimination half-life of about 4.5 hours. In repeated oral administration, the plasma concentration reached a steady state on the 2nd day or later. The plasma concentration was about 40 ng/mL at 2 to 4 hours after the administration in patients treated with long-term administration of 90 mg/day in three divided dose. When this product was administered orally to healthy male adults, the main metabolic pathways were oxidative deamination, oxidative demethylation, deacetylation, and conjugation.

INDICATIONS AND USAGE
- Management of chronic stable angina and angina due to coronary artery spasm.
- Treatment of mild to moderate arterial hypertension.

DOSAGE AND ADMINISTRATION
The dosage needs to be adjusted by titration to individual patient needs. There is limited general clinical experience with doses above 360 mg, but doses upto 540 mg have been studied.

- Dosage must be adjusted to each patient's needs. Starting with 30 mg three times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three daily) at 1- to 2-day intervals until optimum response is obtained.
- In Angina pectoris & variant angina, If the effect is insufficient, the dosage may be increased to 60 mg three times daily.

CONTRAINDICATIONS
Diltiazem is contraindicated in:
- Patients with severe congestive cardiac failure. Symptoms of cardiac failure may be aggravated.
- Patients with sick sinus syndrome (persistent sinus bradycardia) (less than 50 beats/min), sinus arrest, sinoatrial block, etc.) except in the presence of a functioning ventricular pacemaker.
- Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
- Patients with severe hypotension (less than 90 mm Hg systolic).
- Patients who have demonstrated hypersensitivity to the drug.
- Pregnant women or women who may possibly be pregnant.
- patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

ADVERSE REACTIONS
The reported adverse events are: peripheral oedema, nervousness, insomnia, headache, dizziness, atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations, bradycardia, congestive heart failure, ECG abnormality, flushing, hypotension, syncope, tachycardia, ventricular extrasystole, abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paraesthesia, personality change, somnolence, tremor, stomach discomfort, abdominal pain, constipation, dyspepsia, dysgeusia, thirst, gastric pain, nausea, vomiting, diarrhoea, weight gain, hepatic enzymes increase (AST, ALT, LDH, ALP increase), jaundice, petechiae, photosensitivity, pruritus, urticaria, malaise, amblyopia, CPK elevation, dry mouth, dyspnoea, epistaxis, eye irritation, hyperglycaemia, hyperuricemia, impotence, muscle cramps, feeling of muscular weakness, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus, acute generalized exanthematous pustulosis, allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal symptoms, gingival hyperplasia, haemolytic anaemia, increased bleeding time, leukopenia, photosensitivity (including lichenoid keratosis and hyperpigmentation at sun-exposed skin areas), facial flushing, hypersensitivity, erythroderma (exfoliative dermatitis), purpura, retinopathy, myopathy, thrombocytopenia, generalized rash and leukocytoclastic vasculitis.

DRUG INTERACTIONS
Care should be exercised when treating patients with multiple medications.
- Concomitant use of diltiazem hydrochloride and beta-blockers is usually well-tolerated, if combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted.
- Rauwolfia preparations (reserpine, etc.) Bradycardia, atrioventricular block, sinoatrial block, etc. may occur. Pulse rate should be measured periodically, and electrocardiogram should be performed as needed. If any abnormalities are observed, the dosage should be reduced, or administration should be discontinued.
- Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during co-administration and should be based on clinical assessment.
- Anti-H2 agents (cimetidine, ranitidine) Increase in plasma diltiazem concentrations. Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with H2 antagonists. An adjustment in diltiazem daily dose may be necessary.
- It is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over-or under-digitalization.
- Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.
- When used concomitantly, anaesthetics and calcium channel blockers should be titrated carefully.
- Cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued. It is recommended that the ciclosporin dose be reduced, renal function be monitored, circulating ciclosporin levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.
- Concomitant administration of diltiazem with carbamazepine has been reported to result in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for potential drug interaction.
- Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.
- Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered. There is a risk of decrease of diltiazem plasma levels after initiating therapy Rifampin.
- Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended due to the risk of increased cardiac adverse effects due to an additive effect. This combination should only be used under close clinical and ECG monitoring. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.
- Increased risk of bradycardia is associated when Diltiazem coadministered with amiodarone and digoxin. Caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are used.
- Severe bradycardia or heart block may occur by concomitant use of Fingolimod hydrochloride during the initiation. Bradycardia, atrioventricular block, sinus arrest, tremor, dizziness, lightheadedness, etc.) may occur due to increased blood concentrations of Aprindine and diltiazem.
- In all the patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses, because of its increased hypotensive effects and faintness (additive vasodilatating effects). The dosage should be reduced, or administration should be discontinued.
- Rhabdomyolysis or myopathy may occur due to increased blood concentration of simvastatin. Clinical symptoms should be observed periodically.
- Prolonged sleeping time, etc. may occur due to increased blood concentration of triazolam.
- Intensified sedative and hypnotic effects, etc. may occur due to increased blood concentration of midazolam.
- Sleepiness, nausea, vomiting, dizziness, etc. may occur due to increased blood concentration of carbamazepine.
- Effects and toxicity of selegiline hydrochloride may be intensified.
- Nausea, vomiting, headache, insomnia, etc. may occur due to increased blood concentration of theophylline.
- Effects of apixaban may be intensified.
- Effects of vinorelbine tartrate may be intensified.
- Renal disorder, etc. may occur due to increased blood concentration of tacrolimus and ciclosporin.
- Blood concentration of HIV protease inhibitors (ritonavir, saquinavir mesylate, etc.) may increase.
- Anesthetic drugs (isoflurane, enflurane, halothane, etc.) Bradycardia, atrioventricular block, sinus arrest, etc. may occur. Electrocardiogram should be monitored.
- Concurrent use of diltiazem increases exposure to ivabradine and may exacerbate bradycardia and conduction disturbances. Avoid concomitant use of ivabradine and diltiazem.
- When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration. Ataxia, dizziness, nystagmus, etc. may occur due to increased blood concentration of phenytoin. It is recommended that the phenytoin plasma concentrations be monitored.
- Pancuronium bromide, vecuronium bromide, etc., effects of muscle relaxants may be intensified.
- Risk of increase in lithium-induced neurotoxicity.
- Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with diltiazem. Monitor heart rate in patients receiving concomitant diltiazem and clonidine.
- Antiplatelet drugs: Diltiazem was shown to inhibit platelet aggregation. Although the clinical significance of this finding is unknown, potential additive effects when used with antiplatelet drugs should be considered.
- Diltiazem is metabolized by CYP3A4. A moderate (less than 2-fold) increase of diltiazem plasma concentration in cases of co-administration with a stronger CYP3A4 inhibitor has been documented. Grapefruit juice may increase diltiazem exposure (1.2-fold). Patients who consume grapefruit juice should be monitored for increased adverse effects of diltiazem. Grapefruit juice should be avoided if an interaction is suspected. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plasma concentration of co-administered drug. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.
- Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with statins metabolised by CYP3A4 (e.g., atorvastatin, fluvastatin, and simvastatin). An adjustment of the dose of statin may be necessary (see also product information of the relevant statin). When possible, it is recommended to use a statin not metabolised by CYP3A4 (eg. pravastatin) with diltiazem.
- Inhibition of cilostazol metabolism (CYP3A4). Diltiazem has been shown to increase cilostazol exposure and to enhance its pharmacological activity.
- Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.
- Diltiazem can increase methylprednisolone levels (through inhibition of CYP3A4 and possible inhibition of P-glycoprotein) The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.
- Cardiovascular effects of an intravenous bolus of an ionic X-ray contrast media, such as hypotension, may be increased in patients treated with diltiazem. Special caution is required in patients who concomitantly receive diltiazem and X-ray contrast media.

WARNINGS AND PRECAUTIONS:
- Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function.
- Dermatological events may be transient and may disappear despite continued use of diltiazem hydrochloride. Should a dermatologic reaction persist, the drug should be discontinued.
- Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.
- Worsening of congestive heart failure has been reported in patients with pre-existing impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- Decrease in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.
- Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment.
- It has been reported that abrupt cessation of calcium antagonists may aggravate the patient's symptoms. In case where cessation of this product is required, the dosage should be reduced gradually under careful observation of the patient. Patients should be instructed not to discontinue taking this product without consulting physicians.
- Since dizziness, etc. may occur due to antihypertensive action of this product, patients should be cautioned against engaging in potentially hazardous activities such as working at altitude or driving motor vehicles.
- Prolonged QT and ventricular arrhythmia have been reported in coadministration of terfenadine with other antiarrhythmic agents (disopyramide phosphate)

USE IN SPECIAL POPULATION
Pregnancy And Nursing Mothers
Diltiazem should not be administered to pregnant women or women who may possibly be pregnant. Animal studies have shown teratogenicity. Diltiazem is excreted in human milk hence women should not breastfeed while taking diltiazem.

Paediatric population:
Safety and efficacy in children have not been established. Therefore, diltiazem is not recommended for use in children.

Geriatric Use
Reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 of concomitant disease or other drug therapy.

OVERDOSE
In the event of an overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination.
In case of overdosage, administration should be discontinued, and gastric lavage should be performed to remove the product as needed, and the following appropriate therapeutic measures should be taken.
- Bradycardia, complete atrioventricular block: Atropine sulfate hydrate, isoprenaline, etc. should be administered or cardiac pacing should be taken.
- Cardiac failure, hypotension. Cardiotonic drug, vasopressor, infusion, etc. should be administered or assisted circulation should be performed.
  Diltiazem does not appear to be removed by peritoneal or haemodialysis.

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
Herbesser 30mg Tablets: Alu. PVC. Blister Pack of 3 x 10's.
Herbesser 60mg Tablets: Alu. PVC. Blister Pack of 3 x 10's.

ہربیسر®

(ڈیلٹیازیم ہائیڈروکلورائیڈ)

خوراک و ہدایات:

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بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔

خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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