

Product NameAZEMTI 30 mg Tablet

Project Number46389

CountryMalezya

Mock-up Number46389 V2

Date16.04.2024



AZEMTI 30MG TABLET

NAME AND STRENGTH OF ACTIVE INGREDIENTS:

Diltiazem Hydrochloride30mg

PRODUCT DESCRIPTION:

White, flat and cylindrical tablets

PHARMACODYNAMIC:

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Hypertension: Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina: Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reduction in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial.

Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissues. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem causes relaxation of coronary smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and non-ischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data has no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate.

Intravenous diltiazem in doses of 20mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300mg of Diltiazem in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of Diltiazem in doses of up to 240mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation.

PHARMACOKINETICS:

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2% and 4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive in vitro ligand binding studies have also shown diltiazem hydrochloride binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin.

The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentration appear to be in the range of 50 to 200ng/mL. There is departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increases in half-life and 69% increase in bioavailability

in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem is absorbed from the tablet formulation to about 98% of a reference solution. Single oral doses of 30 to 120 mg of Diltiazem tablets results in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration. As the dose of Diltiazem tablets is increased from a daily dose of 120mg (30mg qid) to 240mg (60mg qid) daily, there is an increase in area-under-the-curve of 2.3 times. When the doses are increased from 240mg to 360mg daily, there is an increase in area-under the curve of 1.8 times.

INDICATION:

Diltiazem is indicated for:
- Angina pectoris, variant angina
- essential hypertension (mild to moderate case)

DOSEAGE AND ADMINISTRATION:

- a) Angina pectoris, variant angina
- Usually for adults, 30mg as diltiazem hydrochloride 3 times per day orally. If needed, 30mg may be increased to 60mg
- b) Essential hypertension (mild to moderate case)
- Usually for adults, 30-60mg as diltiazem hydrochloride 3 times per day orally.
- The dose may be adjusted according to the age of the patients and the severity of the symptoms.

CONTRAINDICATION:

Diltiazem Tablet is contraindicated in patients with sick sinus syndrome 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 hypotension (less than 90mmHg systolic), patients who have demonstrated hypersensitivity to the drug, and patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNING AND PRECAUTION:

Cardiac Conduction: Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 4 seconds) after a single dose of 60mg diltiazem.

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in human with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

Hypertension: Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.
Acute Hepatic Injury: 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. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early in therapy (within 1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some.

General: Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, doses of 20mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Pediatric use: Safety and effectiveness in pediatric patients have not been established. Geriatric Use: Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other 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.

DRUG INTERACTION:

Due to potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem.

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450, 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.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetic and calcium blockers should be titrated carefully.

Benzodiazepines: Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4- fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increase (1.5 to 2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g. prolonged sedation) of both midazolam and triazolam.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted.

Bupirone: In nine healthy subjects, diltiazem significantly increased the mean bupirone AUC 5.5 fold and C_{max} 4.1 fold compared to placebo. The T_{1/2} and T_{max} of bupirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of bupirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during co-administration, and should be based on clinical assessment.

Carbamazepine: Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase) resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and single dose of diltiazem 60mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzymes system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. Dose adjustment of diltiazem may be necessary.

Cyclosporine: A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant recipients, a reduction of similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued. The effect of cyclosporine on diltiazem plasma concentration has not been evaluated.

Digibals: Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentration approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitization.

Lovastatin: In a ten-subject study, coadministration of diltiazem (120mg bid diltiazem SR) with lovastatin resulted in a 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma level were not significantly affected by lovastatin or pravastatin.

Quinidine: Diltiazem significantly increases the AUC(0 → ∞) of quinidine by 51%, T_{1/2} by 36%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

Rifampin: Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP 3A4 inducer should be avoided when possible, and alternative therapy considered.

PREGNANCY AND LACTATION:

Pregnancy: Reproduction studies have been conducted in mice, rat, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480mg q.d or 8 mg/kg q.d for 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup

weights, pup survival, as well as prolonged delivery times and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefits justifies the potential risk to the fetus.

Nursing Mothers: Diltiazem is excreted in human milk. One report suggests that concentration in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

SIDE EFFECTS:

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities usually have been excluded.

In hypertension studies; oedema lower limb, sinus congestion and Rash observed more frequently than placebo.

In placebo-controlled angina trials, the incidence of adverse reactions reported during diltiazem therapy was not greater than that reported during placebo therapy. The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to Diltiazem has not been established. The most common occurrences from these studies, as well their frequency of presentation, are edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%) and asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree), bradycardia bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH, thirst, vomiting, weight increase.

Dermatological: Petchiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), astyole, erythema multiforme (including Stevens-Johnsons syndrome, toxic epidermal necrolysis), extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, myopathy, and thrombocytopenia. There have been observed cases of a generalized rash, some characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed, which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and diltiazem therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

SYMPTOMS AND TREATMENT OVERDOSE:

Events observed following diltiazem overdose include bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In additions, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis.

STORAGE CONDITIONS:

Do not store above 30°C.

Protecting from light.

SHELF LIFE:

2 YEARS

PACK SIZE: Pack in PVC/PVDC-Al Blister, pack of 32,48,100,112 tablets.

MANUFACTURED BY:

Gensenta İlaç Sanayi ve Ticaret A.Ş.

Sanayi Caddesi, No:13 Yenibosna,

Bahçelievler, İstanbul/TURKEY

PRODUCT REGISTRATION HOLDER:

MEDİDATA SDN BHD

36, Jin PUS 8/8, Sunway Mentari,

46150 Petaling Jaya, Selangor Darul Ehsan.

Revision Date: 03 April 2024



1300XXXX-X