"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר". עלון מאושר: אפריל 2010
"This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved." Date of approval: April 2010.

DILATAM ®120 SR

SUSTAINED-RELEASE TABLETS

Composition

Each sustained-release tablet contains:

Active Ingredient

Diltiazem hydrochloride 120 mg

Other Ingredients:

Hydroxypropyl methylcellulose, povidone, hydroxypropyl cellulose, talc, polyethylene glycol, colloidal silicon dioxide, hydrogenated vegetable oil, magnesium stearate.

Mechanism of Action

Dilatam 120 SR is a sustained-release tablet formulation offering the advantage of twice daily administration.

Dilatam 120 SR is of particular importance for use in hypertension and angina where it provides convenience and encourages patient compliance.

Diltiazem is a calcium antagonist (slow channel blocker) which inhibits the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle. The resultant pharmacological effects on the cardiovascular system include depression of mechanical contraction of the myocardial and smooth muscle, and depression of both impulse formation (automaticity) and conduction velocity.

Diltiazem dilates the coronary arteries and arterioles, both in normal and ischemic regions, and inhibits coronary artery spasm. This increases myocardial oxygen delivery in patients with vasospastic (Prinzmetal's or variant) angina.

Although diltiazem rarely produces clinically important changes in the rate of sinoatrial (SA) node discharge or recovery time, the drug usually reduces the resting heart rate slightly, especially in patients with SA node disease (e.g. sick sinus syndrome). Diltiazem also slows atrioventricular (AV) node conduction and prolongs refractoriness, thereby prolonging the AH (Atria-His bundle) interval. This usually results in PR prolongation on ECG and may rarely cause second- or third-degree AV block.

Dilatam 120 SR produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Dilatam 120 SR decreases vascular resistance, increases cardiac output (by increasing stroke volume) and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity on the renin-angiotensin-aldosterone axis has been observed. Dilatam 120 SR antagonizes the renal and peripheral effects of angiotensin II.

Indications

Hypertension

Dilatam 120 SR may be used either as monotherapy or with other antihypertensive medications such as diuretics.

Angina Pectoris

- Chronic stable angina.
- Angina due to coronary artery spasm.

Contraindications

Known hypersensitivity to the drug or to any other ingredient of the preparation..

Pregnancy and women of childbearing capacity.

Breastfeeding.

Sick sinus syndrome or second or third degree AV block, except in the presence of a functioning ventricular pacemaker.

Hypotension (less than 90 mm Hg systolic).

Congestive heart failure.

Sever bradycardia (below 40 beats per minute).

Left ventricular failure with pulmonary congestion.

Acute myocardial infarction and pulmonary congestion, documented by X-ray on admission.

Concurrent use with dantrolene infusion because of the risk of ventricular fibrillation (see Drug Interactions)

Warnings

Hypotension

Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

Congestive Heart Failure

Although diltiazem has a negative inotropic effect *in vitro*, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index or consistent negative effects on contractility.

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 β-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

Cardiac Conduction

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with a first degree AV block detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome), or second or third degree AV block (0.4%). A patient with Prinzmetal's angina developed periods of asystole (2-5 seconds) after a single dose of 60 mg diltiazem. Concomitant use of diltiazem with β-blockers or digitalis may result in additive effects on cardiac conduction.

Acute Hepatic Injury

In rare instances, symptoms consistent with acute hepatic injury including significant elevations in enzymes such as alkaline phosphatase, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), have occurred with diltiazem. These were reversible on drug discontinuation. Drug relationship was uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however cholestasis, with or without jaundice, has been reported. Rare instances of allergic hepatitis have been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility.

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100mg/kg/day.

Use in Pregnancy

(see Contraindications)

Reproduction studies have been conducted in mice, rats and rabbits. Administration of doses ranging from 5-10 times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. In some studies, these doses have been reported to cause skeletal abnormalities. In peri- and post-natal studies, there was some reduction in early pup weights and survival rates. There was an increased incidence of stillbirth at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women. . Also, dilitazem is a calcium channel blocker and drugs listed in this class carry the potential for fetal hypoxia aswsociated with maternal hypotension. Therefore, diltiazem must not be used in pregnancy or women of childbearing potential.

Use in Breastfeeding

(see Contraindications)

Diltiazem is excreted in human milk. Diltiazem levels were measured in both serum and milk in lactating women. One report suggests that concentrations in breast milk may approximate serum levels. These data show that diltiazem is freely diffusible in milk but it is not known whether it is harmful to the newborn. Therefore, breastfeeding while taking this drug should be avoided.

Use in Pediatrics

Safety and efficacy of the use of diltiazem in children have not been established.

Use in the Elderly

The half life of calcium channel blockers may be increased in the elderly as a result of decreased clearance. Therefore caution should be exercised in this patient group. Increase in plasma concentrations may be associated with increase in incidence of adverse reactions (approximately 13% higher in this group). Those adverse reactions which occur more frequently include: peripheral oedema, bradycardia, palpitation, dizziness, rash and polyuria.

Impaired Renal Function

Although the pharmacokinetic profile of diltiazem in patients with impaired renal function is similar to that in patients with normal renal function, caution is still advised.

Impaired Hepatic Function

Since diltiazem is extensively metabolized by the liver, it should be used with caution in patients with impaired hepatic function or reduced hepatic blood flow.
Dosing reduction may be necessary.

Adverse Reactions

Adverse reactions are generally not serious and rarely require discontinuation of therapy or dosage adjustment. In clinical trials of diltiazem and diltiazem SR formulations involving over 3200 patients, the most common events (i.e, greater than 1%) were edema (4.6%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), dyspepsia (1.2%), palpitations, lower limb oedema, constipation, gastric pain, malaise and erythema.

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials.

Cardiovascular System

Peripheral edema, hypotension, palpitations, syncope, AV block (1st, 2nd or 3rd degree), bradycardia, congestive heart failure, arrhythmia (unspecified), pulmonary edema, angina, tachycardia, abnormal ECG, ventricular extrasystoles.

Central Nervous System

Dizziness, lightheadedness, nervousness, sleep disturbances, psychiatric disturbances (depression, amnesia, paranoia, psychosis, hallucinations, personality changes), headache, weakness, shakiness, jitteriness, paresthesia, somnolence, asthenia, insomnia, abnormal dreams, tinnitus, tremor/hand tremor.

Gastrointestinal

Anorexia, nausea, diarrhea, constipation, abdominal discomfort, abdominal cramps, dyspepsia, disgeusia, hepatic enzyme increase (AST, ALT, LDH, ALP), vomiting, dry mouth, thirst, weight increase..

Dermatological

Dermatitis, rash, pruritus, urticaria, hair loss, photosensitivity, erythema multiforme, Stevens-Johnson syndrome.

Hematopoietic

Leukopenia, petechiae, ecchymosis, purpura, bruising, hematoma.

Other

Flushing, nasal congestion, chest congestion, sinusitis, rhinitis, gingival hyperplasia, micturition disorders (e.g. polyuria, nocturia, dysuria), sexual difficulties, impotence, shortness of breath, dyspnea, wheezing, joint stiffness, pain, arthritis, gynecomastia, hyperglycemia, hyperuricemia, weight gain, epistaxis, anorexia, muscle cramps, CPK increase, osteoarticular pain.

In addition to the adverse effects listed above, the following have been reported: gait abnormality, tremor, amblyopia, eye irritation, bundle branch block, and amnesia.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: mood changes (including deprerssion), sino-atrial block, congestive heart failure, photosensitivity, hepatitis, musculo-cutaneous reactions such as simple erythema or occasionally desquamative erythema with or without fever, angioneurotic edema, symptoms of vasodilation (such as flushing, lower limb edema, sweating), alopecia, erythema multiforme (including rare cases of Steven-Johnson's syndrome), exfoliative dermatitis, extrapyramidal symptoms, acute generalized exanthematous pustular dermatitis, orthostatic hypotension, malaise, gastric pain, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy and thrombocytopenia. Very rare cases of toxic epidermal necrolysis have also been reported 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 number of well-documented cases of generalized rash, characterized as leukocyloclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

Precautions

Diltiazem 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.

Dermatological Events

Dermatological 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.

Use in Diabetics

Diltiazem should be used with caution in patients suffering from diabetes. Like other calcium channel blockers, diltiazem influences insulin secretion and its peripheral action by inhibiting calcium influx into cells. In one study, increases in fasting and peak glucose levels were observed after 2 to 6 months of diltiazem administration.

Other Effects

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.

Like other calcium channel antagonists, diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk to develop an intestinal obstruction.

Abrupt Withdrawal

The sudden withdrawal of dilitazem has been associated with sever angina in anginal patients.

Effects on Ability to Drive and Use Machines

Diltiazem may cause adverse reactions such as dizziness, which may impair patients' ability to drive or operate machinery to a varying extent depending on the dosage and individual susceptibility. Therefore, patients should not drive or operate machinery if affected.

Drug Interactions

Note:

Due to the 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.

Diltiazem is extensively metabolised by CYP3A4, and as a result serum levels of diltiazem may be:

• Increased by concomitant usage of CYP3A4 inhibitors such as H2 antagonists (e.g. cimetidine, ranitidine) and protease inhibitors (e.g. atazanavir, ritonavir)

• Decreased by concomitant usage of CYP3A4 inducers such as barbiturates (phenobarbital, primidone), phenytoin and rifampicin.

Diltiazem is also an inhibitor of CYP3A4, and may therefore increase serum levels of CYP3A4 substrates such as benzodiazepines (especially midazolam and triazolam), carbamazepine, ciclosporin, cilostazol, ivabradine, statins (simvastatin, atorvastatin, lovastatin), sirolimus, tacrolimus and theophylline. Care should be exercised in patients taking these drugs. Concomitant use of diltiazem with cilostazol and ivabradine should be avoided.

Diltiazemβ-adrenergic Blockers/Calcium Channel Blockers: β-adrenergic blockers and calcium channel blockers both have negative chronotropic and inotropic effects. These combinations are advantageous in some patients (e.g. hypertension, angina); however, they may be a problem in others (e.g. sinoatrial disease, conduction defects, heart failure) (see Warnings).

Combination therapy can, however adversely affect cardiac function, because of the depressant effects on myocardial contractility or AV conduction. Therefore, if combined therapy is used, closely monitor the patient and reassess continued use periodically Patients with pre-existing conduction defects should not receive the combination of diltiazem and beta-blockers.

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

In contrast, there appears to be no effect on the pharmacokinetics of atenolol, a renally cleared drug. In view of the known pharmacodynamic interactions between these classes of drugs, this effect may be of clinical relevance.

Dilitazem/Drugs which May Induce Bradycardia/Other Antiarrhythmic Drugs (e.g. Amiodarone):

There may be an additive effect (increased depression of cardiac conduction with risk of bradycardia and AV block) when diltiazem is prescribed with drugs which may induce bradycardia or other anti-arrhythmic drugs (e.g. amiodarone and beta blockers).

Amiodarone should be used with caution with diltiazem particularly if there is suspicion of underlying dysfunction of the sinus node, such as bradycardia or sick sinus syndrome or if there is partial A-V block. Sinus arrest and a life-threatening low cardiac output state developed when amiodarone was added to a regimen of diltiazem and a diuretic. It has been suggested that diltiazem and amiodarone have additive adverse effects on sinus node function and myocardial contractility. There is an increased risk of bradycardia with this combination. Caution is required when amiodarone is combined with diltiazem, particularly in the elderly and when high doses are used.

Diltiazem/Rifampicin: There is a risk of decreased diltiazem plasma levels after initiating therapy with rifampicin. The patient should be carefully monitored when initiating or discontinuing rifampicin treatment.

Diltiazem/Benzodiazepines (e.g. Midazolam, Triazolam, Diazepam): Diltiazem significantly increases plasma concentration of midazolam and triazolam and prolongs their half-life. Special care should be taken when prescribing short-acting benzodiazepines metabolised by the CYP3A4 pathway in patients using diltiazem.

Diazepam has been reported to cause a significant decrease in diltiazem plasma levels. The average decrease in diltiazem concentration was between 20 and 30%. Three out of eight patients showed decreases which were greater than 50%.

Diltiazem/Buspirone: In 9 healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5-fold and Cmax 4.1-fold compared to placebo. The T½ and Tmax of buspirone were not significantly affected by diltiazem. 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

Dilitazem/ Corticosteroids (e.g Methyprednisolone): Concomitant administration has resulted in the inhibition of methylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein. The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary

Diltiazem/Alpha Blockers: Concomitant treatment with alpha-blockers may produce or aggravate hypotension. The combination of diltiazem with an alpha-blocker should only be considered with the strict monitoring of blood pressure due to the risk of increased antihypertensive effects.

Diltiazem/Rimonabant: Co-administration with diltiazem results in an increase in serum rimonabant levels.

Diltiazem/Short and Long Acting Nitrates: Increased hypotensive effects and faintness may be seen due to additive vasodilatating effects. In patients treated with calcium channel antagonists, the addition of nitrate derivatives should only be carried out at gradually increasing doses.

Diltiazem/Phenobarbital/Phenytoin: As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem, in order to maintain optimum therapeutic blood levels.

Diltiazem/Quinidine/Theophylline/Carbamazepine: Pharmacologic effects may be increased due to inhibition of hepatic metabolism possibly by diltiazem. The increased plasma levels cause neurotoxic symptoms which resolve several days after stopping the calcium blocker. 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.

Diltiazem/Tricyclic Antidepressants: Diltiazem may increase the bioavailability of tricyclic antidepressants.

Diltiazem/Cimetidine/Ranitidine: Cimetidine or ranitidine increase the bioavailability of diltiazem. Patients on diltiazem should be monitored closely when adding cimetidine or ranitidine and, if necessary, the dose of diltiazem should be reduced.

Diltiazem/Statins: Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis due to statins metabolised by CYP3A4 may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.
Diltiazem/Cyclosporin*:* Cyclosporin plasma levels may be increased by diltiazem, and renal toxicity may occur. Therefore, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.
Diltiazem/Lithium: Diltiazem and lithium appear to act synergistically. Neurotoxicity has occurred with coadministration, even when the lithium level was in the therapeutic range.
Diltiazem/Digoxin: Serum digoxin levels may be increased upon concomitant administration of calcium channel blockers and digoxin. Although some studies suggest that no significant interaction occurs with diltiazem, caution is required and digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over or underdigitalization.
Diltiazem/Anticoagulants/Aspirin/Salicylates: Anticoagulants, aspirin and salicylates are highly protein-bound drugs. Caution should be exercised upon concomitant administration with diltiazem, since serum levels of these agents may be increased.
Diltiazem/Antihypertensive Agents (e.g.: ACE Inhibitors) /Alcohol: Additive hypotensive effects may result upon concomitant administration. Therefore, caution should be exercised, and dosage adjustments of either agents may be necessary.
Diltiazem/Inhalation Anesthetics*:* Concurrent use with calcium channel blockers may produce additive hypotensive effects. Therefore, caution should be exercised when inhalation anesthetics are administered during surgery, to patients on dialtiazem.
Diltiazem/Encainide*:* Serum encainide levels may be increased without any change in the levels of the active metabolites of encainide.
Diltiazem/Fentanyl: Severe hypotension or increased fluid volume requirements have occurred in patients receiving nifedipine and fentanyl concomitantly; this interaction should also be considered for all calcium blockers.
Diltiazem/Dantrolene Infusion: Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of a calcium channel antagonist and dantrolene is therefore potentially dangerous.

Dosage and Administration

Note: Dilatam 120 SR Tablets are not suitable for use in patients who require less than 120 mg per dose, since the tablet is not divisible.

Hypertension

The usual recommended dosage of Dilatam 120 SR Tablets is one tablet twice daily. The dosage should be individualized and adjusted to the patient's needs.

The maximum antihypertensive effect is achieved usually by 14 days of chronic therapy. The usual optimum dosage range reported in clinical trials was 240-360 mg/day.

Angina Pectoris

The usual recommended dosage of Dilatam 120 SR Tablets is one tablet twice daily. The dosage should be individualized and adjusted to the patient's needs.

Concomitant Drug Therapy

An additive antihypertensive effect occurs when diltiazem is coadministered with other antihypertensives. Adjust the dose of Dilatam 120 SR or the concomitant antihypertensive accordingly.

Sublingual nitroglycerin may be taken as required to abort acute anginal attacks during Dilatam 120 SR therapy. Dilatam 120 SR may be also coadministered with prophylactic nitrate therapy.

Overdosage

The oral LD50 in mice and rats ranged from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD50 in these species was 60 and 38 mg/kg, respectively. The oral LD50 in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. Toxic diltiazem blood levels in man are not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases. There have been 29 cases of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions. Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports

Manifestations

Nausea, weakness, dizziness, drowsiness, confusion, and slurred speech. Marked and prolonged hypotension (possibly leading to collapse) and bradycardia (with or without isothythmic dissociation), both of which may result in decreased cardiac output. Junctional rhythms and second- or third-degree AV block, , cardiac failure, and atrioventricular conduction disturbances may be seen. Death has occurred.

Treatment

If the patient is seen shortly after oral ingestion, employ emetics or lavage and cathartics. Treatment is supportive. β-adrenergic agents or IV calcium have been used effectively. Although calcium appears to reverse adverse hemodynamic effects, it may not always reverse electrophysiological toxicity. Cardiac failure is treated with inotropic agents (isoproterenol, dopamine or dobutamine) and diuretics.

Monitor cardiac and respiratory function. In patients with hypertrophic cardiomyopathy (IHSS), use α-adrenergic agents (phenylephrine hydrochloride, metaraminol bitartrate or methoxamine HCl) to maintain blood pressure; avoid isoproterenol and norepinephrine. Since these agents are highly protein bound, dialysis is not likely to help.

The following are treatment guidelines for acute cardiovascular adverse reactions:

Symptomatic Hypotension Requiring Treatment

Primary treatment (by IV route) consists of dopamine, norepinephrine, metaraminol, isoproterenol or calcium . Supportive treatment consists of IV fluids administered in the Trendelenburg position.

Bradycardia, AV Block, Systole

Primary treatment (by IV route) consists of isoproterenol or norpinephrine (not in patients with IHSS), atropine sulfate,(0.6-1 mg) calcium gluconate (10% solution), and, in addition, cardiac pacing. Supportive treatment consists of IV fluids (slow drip).

Rapid Ventricular Rate Due to Antegrade Conduction in Flutter/Fibrillation with Wolff-Parkinson-White or Lown-Ganong-Levine Syndromes

Primary treatment consists of DC cardioversion and procainamide or lidocaine (by IV route). Supportive treatment consists of IV fluids (slow drip).

Storage

Store in a dry and dark place, below 25°C.

Registration Number

057.29.26825.00

Manufacturer

Teva Pharmaceutical Industries Ltd
P.O.Box 3190, Petach Tikva
For
Abic Ltd
P.O.Box 8077, Kiryat Nordau, Netanya