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NAME OF THE MEDICINAL PRODUCT:

DILTIAZEM TEVA®

PHARMACEUTICAL FORM:
Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Diltiazem Teva 30
Active Ingredient:
Diltiazem hydrochloride 30 mg

Others Ingredients
Lactose monohydrate, hydroxypropyl methylcellulose, povidone, magnesium stearate, macrogol/peg 400, FD&C yellow #6/sunset yellow FCF aluminium lake, titanium dioxide, polysorbate 80, purified water.

Diltiazem Teva 60
Active Ingredient:
Diltiazem hydrochloride 60 mg

Others Ingredients
Lactose monohydrate, hydroxypropyl methylcellulose, povidone, magnesium stearate, polysorbate 80, FD&C yellow #6/sunset yellow FCF aluminium lake, macrogol/peg 400, titanium dioxide, purified water.

CLINICAL PARTICULARS:

Indications

Angina Pectoris due to Coronary Artery Spasm
Diltiazem is indicated in the treatment of angina pectoris due to coronary artery spasm. It has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).

Chronic Stable Angina (Classic Effort-Associated Angina)
Diltiazem is indicated in the management of chronic stable angina. It is also effective in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. In short-term controlled trials, Diltiazem has been effective in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

Dosage and Administration

Dosage should be individualized. Start with 30 mg 4 times daily, before meals and at bedtime. The dosage should be gradually increased to 240 mg (given in equal, divided doses 3-4 times daily) at 1-2-day intervals, until optimum response is obtained.

There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titrate with particular caution.

Concomitant Drug Therapy

Sublingual nitroglycerin may be taken as required to abort acute anginal attacks during diltiazem therapy. Diltiazem may be safely co-administered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the anti-anginal effectiveness of this combination. For use with β-blockers or digoxin, see Precautions.

Use with caution in titrating dosages in patients suffering from impaired renal or hepatic function, since dosage requirements are not available.

Mechanism of Action

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.

Following oral administration, diltiazem is about 80-90% absorbed with a single absolute bioavailability of 40-67%. Onset of action occurs 30 minutes after an oral dose, with peak plasma levels occurring after 2-3 hours. Plasma protein binding is 70-80%. Plasma elimination half-life is 3.5-9 hours. Therapeutic serum levels are in the range of 0.04-0.2 mcg/ml.

Diltiazem is subject to extensive first pass hepatic metabolism, the main metabolite being deacetyl-diltiazem. This metabolite is present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent a coronary vasodilator as diltiazem. About 2-4% of the drug is excreted unchanged in the urine.

Contraindications

- Known hypersensitivity to the drug or to any other ingredient of the preparation.
- 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 section "Drug Interactions").

- Combination with ivabradine (see section "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.

General Anesthesia

In the case of general anaesthesia, the anaesthetist must be informed that the patient is taking diltiazem. The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Psychic Effects

Treatment with diltiazem may be associated with mood changes, including depression. Early recognition of relevant symptoms is important, especially in predisposed patients. In such cases, drug discontinuation should be considered.

Gastrointestinal Effects

Diltiazem has an inhibitory effect on intestinal motility. Therefore it should be used with caution in patients at risk of developing an intestinal obstruction.

Diabetes Mellitus

Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

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

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 very limited data from the use of diltiazem in pregnant patients. Therefore, diltiazem is not recommended during pregnancy or in women of childbearing potential not using effective contraception.

Use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Use in Breastfeeding

(see Contraindications)

Diltiazem is excreted in breast 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 is contraindicated.

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.

Increase of plasma concentrations of diltiazem may be observed in the elderly and patients with renal or hepatic Insufficiency . The contraindications and precautions should be carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment

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. Increase of plasma concentrations of diltiazem may be observed in the elderly and patients with renal or hepatic Insufficiency . The contraindications and precautions should be carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment

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 (including lichenoid keratosis at sun exposed skin areas),,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, vomiting 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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 paqtients.

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

Notes:

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, erythromycin and theophylline. Care should be exercised in patients taking these drugs. Concomitant use of diltiazem with cilostazol should be avoided.

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine (see section “Contraindications”).

Diltiazem/β-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.

Overdosage

The oral LD_{50} in mice and rats ranged from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50} in these species was 60 and 38 mg/kg, respectively. The oral LD_{50} 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).

Registration Numbers

Diltiazem Teva 30 mg: 140 85 27958 00
Diltiazem Teva 60 mg: 140 86 27957 00

Storage:

Store in a dry place below 25°C.

Manufacturer

Teva Pharmaceutical Industries Ltd
P.O.Box 3190, Petach Tikva