PRODUCT MONOGRAPH

[Pr]TEVA-DILTIAZEM

(diltiazem hydrochloride)

Tablets

30 mg and 60 mg

Antianginal Agent

Teva Standard

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ACTION AND CLINICAL PHARMACOLOGY

TEVA-DILTIAZEM tablet is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist).

Mechanism of Action

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the cells through specific ion channels. Diltiazem blocks transmembrane influx of calcium through the slow channel without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Diltiazem does not alter total serum calcium.

Angina: The precise mechanism by which diltiazem relieves angina has not been fully determined but it is believed to be brought about largely by its vasodilator action. In angina due to coronary spasm, diltiazem increases myocardial oxygen delivery by dilating both large and small coronary arteries and by inhibiting coronary spasm at drug levels which cause little

negative inotropic effect. The resultant increases in coronary blood flow are accompanied by dose dependent decreases in systemic blood pressure and decreases in peripheral resistance.

In angina of effort it appears that the action of diltiazem is related to the reduction of myocardial oxygen demand. This is probably caused by a decrease in blood pressure brought about by the reduction of peripheral resistance and of heart rate.

Hypertension: The antihypertensive effect of diltiazem is believed to be brought about largely by its vasodilatory action on peripheral blood vessels with resultant decrease in peripheral vascular resistance.

Hemodynamic and Electrophysiologic Effects

Diltiazem produces antihypertensive effects both in the supine and standing positions. Resting heart rate is usually slightly reduced. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually unaffected. Heart rate at maximum exercise is reduced.

Studies to date, primarily in patients with normal ventricular function, have shown that cardiac output, ejection fraction and left ventricular end-diastolic pressure have not been affected.

Chronic therapy with diltiazem produces no change, or an increase, in circulating plasma catecholamines. However, no increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem inhibits the renal and peripheral effects of angiotensin II.

In man intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. Chronic oral administration of diltiazem in doses up to 540 mg per day has resulted in small increases in PR interval. Second degree and third degree AV block have been observed (see WARNINGS). In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Pharmacokinetics

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect giving absolute bioavailability (compared to intravenous dosing) of about 40%. Therapeutic blood levels appear to be in the 50-200 ng/mL range and the plasma elimination half-life (beta-phase) following single or multiple drug administration is approximately 3.5 to 6.0 hours. *In vitro* human serum binding studies revealed that 70 to 80% of diltiazem is bound to plasma proteins. Diltiazem undergoes extensive hepatic metabolism in which only 2-4% of the drug appears unchanged in the urine and 6-7% appears as metabolites. The metabolic pathways of diltiazem include N- and O-demethylation (via cytochrome P-450), deacetylation (via plasma and tissue esterases), in addition to conjugation (via sulfation and glucuronidation). *In vitro* studies have demonstrated that CYP 3A4 is the principal CYP isoenzyme involved in N-demethylation. The major metabolite, desacetyl diltiazem, is present in the plasma at levels 10-20% of the parent drug and is 25-50% as potent as diltiazem in terms of coronary vasodilation.

Diltiazem Tablets: Single oral doses of 30 to 120 mg of diltiazem tablets result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration. There is a departure from linearity of accumulation of diltiazem when diltiazem tablets are administered to steady-state in normal subjects. A 240 mg daily dose (60 mg QID) gave plasma levels 2.3 times higher than a 120 mg daily dose (30 mg QID) and a 360 mg daily dose (90 mg QID) had levels 1.7 times higher than the 240 mg daily dose.

Diltiazem SR (Twice-a-day) Capsules: Diltiazem is absorbed from the sustained release (SR) capsule formulation to about 93% of the tablet form at steady-state. A single 120 mg dose of the capsule resulted in detectable plasma levels within 2 to 3 hours and peak plasma levels at 7 to 11 hours. The apparent elimination half-life after single or multiple dosing is 5 to 7 hours. A departure from linearity similar to that observed with the diltiazem tablet is observed. As the dose of diltiazem SR capsules is increased from a daily dose of 120 mg (60 mg BID) to 240 mg (120 mg BID) daily, there is an increase in bioavailability of 2.6 times. When the dose is increased from 240 mg to 360 mg daily there is an increase in bioavailability of 1.8 times. The

average plasma levels of the capsule dosed twice daily at steady-state are equivalent to the tablet dosed four times daily when the same total daily dose is administered.

A study which compared patients with normal hepatic function to liver cirrhosis patients noted an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single dose study in patients with severely impaired renal function showed no difference in the half-life of diltiazem as compared to patients with normal renal function. (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

A comparative steady-state bioavailability study was performed on TEVA-DILTIAZEM 60 mg Tablets and Cardizem® 60 mg Tablets. After three days of drug administration, steady-state plasma diltiazem concentrations were achieved and the following pharmacokinetic plasma data (mean ± standard deviation) calculated for the TEVA-DILTIAZEM and Cardizem® formulations is tabulated from plasma diltiazem concentrations –measured following a single oral dose on day

	TEVA-DILTIAZEM 60 mg	Cardizem® 60 mg
Area Under the Curve (ng·hours/ml): 0-30 hours	1114.27 ± 450.13	1106.50 ± 332.16
Peak Concentration: C_{max} (ng/ml)	135.77 ± 51.16	143.13 ± 42.35
Time of Peak Level: T_{max} (hours)	3.00 ± 0.79	2.90 ± 0.79
Elimination Half-Life: $t_{½}$ (hours)	5.18 ± 1.87	5.21 ± 1.78
Elimination Rate Constant: K_{el} ($hour^{1}$)	0.152 ± 0.055	0.148 ± 0.049

INDICATIONS AND CLINICAL USE

Angina:

1. TEVA-DILTIAZEM (diltiazem hydrochloride) tablets may be used in the management of angina resulting from coronary artery spasm.

2. TEVA-DILTIAZEM tablets are indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

3. TEVA-DILTIAZEM tablets may be useful in unstable angina when spasm of the coronary vessels is definitely a contributing factor (e.g. ST segment elevation). In the absence of objective evidence of a spastic component, nitrates or nitrates plus a beta-blocker are at present the treatment of choice. If, in the view of a cardiologist, the addition of TEVA-DILTIAZEM to this regimen is considered necessary and safe, then the use of TEVA-DILTIAZEM tablets might be considered. Generally, the patient should be hospitalized and treatment initiated under the supervision of a cardiologist.

TEVA-DILTIAZEM tablets may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, patients must be monitored closely (See WARNINGS).

CONTRAINDICATIONS

TEVA-DILTIAZEM (diltiazem hydrochloride) Tablets are contraindicated:

1. In patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker;

2. In patients with second or third degree AV block;

3. In patients with known hypersensitivity to diltiazem;

4. In patients with severe hypotension (less than 90 mm Hg systolic);

5. In myocardial infarction patients, who have left ventricular failure manifested by pulmonary congestion.

6. In pregnancy and in women of child-bearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals. In repeated dose studies a high incidence of vertebral column malformations were present in the offspring of mice receiving more than 50 mg/kg of diltiazem HCI orally.

In the offspring of mice receiving a single oral dose of 50 or 100 mg/kg on day 12 of gestation, the incidence of cleft palate and malformed extremities was significantly higher. Vertebral malformations were most prevalent when they received the drug on day 9. In rats, a significantly higher fetal death rate was present when 200 and 400 mg/kg were given orally on days 9 to 14 of gestation. Single oral dose studies in rats resulted in a significant incidence of skeletal malformations in the offspring of the group receiving 400 mg/kg on day 11. In rabbits, all pregnant dams receiving 70 mg/kg orally from day 618 of gestation aborted; at 35 mg/kg, a significant increase in skeletal malformations was recorded in the offspring (See TOXICOLOGY - Reproduction Studies).

WARNINGS

Cardiac Conduction

TEVA-DILTIAZEM (diltiazem hydrochloride) Tablets prolong 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 (6 of 1208 patients or 0.5%).

Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.

Congestive Heart Failure

Because diltiazem has a negative inotropic effect *in vitro* and it affects cardiac conduction, the drug should only be used with caution and under careful medical supervision in patients with congestive cardiac failure. (see also CONTRAINDICATIONS).

Use with Beta-blockers

The combination of diltiazem and beta-blockers warrants caution since in some patients additive effects on heart rate, AV conduction, blood pressure or left ventricular function have been observed. Close medical supervision is recommended.

Generally, diltiazem should not be given to patients with impaired left ventricular function while they receive beta-blockers. However, in exceptional cases when, in the opinion of the physician, concomitant use is considered essential, such use should be instituted gradually in a hospital setting.

Diltiazem gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Hypotension

Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension. In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of diltiazem should be taken into consideration.

Patients with Myocardial Infarction

Use of immediate release diltiazem at 240 mg per day started 3 to 15 days after a myocardial infarction was associated with an increase in cardiac events in patients with pulmonary

congestion, and no overall effect on mortality. Although there has not been a study of diltiazem hydrochloride capsules in acute myocardial infarction reported, its use may have effects similar to those of immediate release diltiazem in acute myocardial infarction.

Acute Hepatic Injury

In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury have been observed. These reactions have been reversible upon discontinuation of drug-therapy. Although a causal relationship to diltiazem has not been established in all cases, a drug induced hypersensitivity reaction is suspected (see ADVERSE REACTIONS). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

PRECAUTIONS

Impaired Hepatic or Renal Function

Because TEVA-DILTIAZEM (diltiazem hydrochloride) Tablets are extensively metabolized by the liver and excreted by the kidney and in bile, monitoring of laboratory parameters and cautious dosage titration are recommended in patients with impaired hepatic or renal function. (See ADVERSE REACTIONS).

Pediatric Use

The safety of diltiazem in children has not yet been established.

Nursing Mothers

Diltiazem has been reported to be excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. Since diltiazem safety in newborns has not been established, it should not be given to nursing mothers.

Use in the Elderly

Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include: peripheral edema, bradycardia, palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable (see DOSAGE AND ADMINISTRATION).

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P450 system. Coadministration of diltiazem with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, theophylline.

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, anesthetics and calcium channel blockers should be titrated carefully.

Benzodiazepines: Diltiazem significantly increases peak plasma levels and the elimination half-life of triazolam and midazolam.

Beta-blockers: The concomitant administration of diltiazem with beta adrenergic blocking drugs warrants caution and careful monitoring. Such an association may have an additive effect on heart rate, on AV conduction or on blood pressure (See WARNINGS). Appropriate dosage adjustments may be necessary. A study in five normal subjects showed that diltiazem increased propranolol bioavailability by approximately 50%.

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 a single dose of oral diltiazem 60 mg: Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme 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. An adjustment in the diltiazem dose may be warranted.

Cyclosporine: A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations 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 concentrations has not been evaluated.

Digitalis: Diltiazem and digitalis glycosides may have an additive effect in prolonging AV conduction. In clinical trials, concurrent administration of diltiazem and digoxin have resulted in increases in serum digoxin levels with prolongation of AV conduction. This increase may result from a decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should be carefully monitored. The dose of digoxin may need downward adjustment.

Rifampin: Administration of diltiazem with rifampin markedly reduced plasma diltiazem concentrations and the therapeutic effect of diltiazem.

Short and Long-acting Nitrates: Diltiazem may be safely co-administered with nitrates, but there have been few controlled studies to evaluate the antianginal effectiveness of this combination.

Other Calcium Antagonists: Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil or to nifedipine, using diltiazem in conjunction with either of these drugs may be beneficial.

ADVERSE REACTIONS

(See also OVERALL DILTIAZEM SAFETY PROFILE)

A. Diltiazem Tablets

A safety evaluation was carried out in controlled clinical trials with 1208 North American angina patients, some of whom were severely ill and were receiving multiple concomitant therapy. Adverse effects were reported in 19.6% of patients and required discontinuation of treatment in 7.2%.

The most common occurrences and their frequency are: nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%) (AV block, bradycardia, tachycardia and sinus arrest), headache (2.0%), rash (1.8%) and asthenia (1.1%).

In addition, the following events were reported in less than 1.0% of cases: Cardiovascular: Angina, bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope. A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately 5 hours after receiving a single 60 mg dose of diltiazem.

Nervous System: Amnesia, confusion, depression, dizziness, drowsiness, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, tremor, weakness.

Gastrointestinal: Anorexia, constipation, diarrhea, dyspepsia, vomiting.

Dermatologic: Petechiae, pruritus, urticaria.

Other: Amblyopia, decreased sexual performance, dysgeusia, dyspnea, epistaxis, eye irritation, hyperglycemia, nocturia, osteo-articular pain, parasthesia, photo-sensitivity, polyuria, thirst, tinnitus, weight increase.

Rarely, reports of extremely elevated liver enzymes, cholestasis, hyperbilirubinemia, jaundice, epigastric pain, anorexia, nausea, vomiting, stool discoloration, dark urine and weight loss have been reported. The symptoms and laboratory test abnormalities have been reversible on drug discontinuation (see WARNINGS).

Two incidents of marked hyperglycemia, hyperkalemia, bradycardia, asthenia, hypotension and gastrointestinal disturbances have been reported in diabetic patients receiving diltiazem, glyburide and a beta-blocker along with several other medications. Drugs were discontinued and

supportive measures were administered which resulted in the patients fully recovering within a few days.

Laboratory Tests: In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH and CPK, have been noted during diltiazem therapy.

B. <u>Diltiazem SR (Twice-a-day) Capsules</u>

A safety evaluation was carried out in controlled and open label studies in 611 hypertensive patients treated with diltiazem SR capsules either alone or in combination with other antihypertensive agents. Adverse effects were reported in 34.2% of patients and required discontinuation of therapy in 7.2 %.

The most common adverse effects were: peripheral edema (8.3%); headache (4.9%); dizziness (4.7%); asthenia (3.9%), vasodilation (flushing) (2.3%) and bradycardia (2.1 %).

The following percentage of adverse effects, divided by system, was reported:

Cardiovascular: Edema peripheral (8.3%), vasodilation (flushing) (2.3%), bradycardia (2.1 %), AV Block (first degree) (1.6%), palpitations (1.3%), arrhythmia (1.0%), heart failure right (0.5%).

Central Nervous System: Headache (4.9%), dizziness (4.7%), asthenia (3.9%), somnolence (1.0%), nervousness (anxiety) (0.8%), paresthesia (0.7%), insomnia (0.5%), depression (0.5%), dream abnormality (O.5%), tinnitus (0.5%).

Gastrointestinal: Dyspepsia (1.1%), nausea (1.1 %), constipation (0.7%).

Dermatological: Rash (1.6 %)

Laboratory Tests: Increased alkaline phosphatase (0.7%)

Other: Impotence (1.6%), musculoskeletal pain (1.5%), nocturia (1.1 %), polyuria (1.0%), rhinitis (0.5%).

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: syncope, AV block, postural hypotension, chest pain, dyspnea, tremor, gait abnormality, vertigo, taste alteration, anorexia, increased appetite, dry mouth, vomiting, diarrhea, increased saliva, acute hepatic injury, pruritus, urticaria, conjunctivitis, amblyopia, ejaculation abnormality, malaise, fever.

The following abnormal laboratory findings have been rarely reported: increased SGOT/SGPT, bilirubinemia, hyperproteinemia, hypercholesteremia, hyperlipidemia, hyperglycemia, hypokalemia, urine abnormality (see PRECAUTIONS).

OVERALL DILTIAZEM SAFETY PROFILE

In clinical trials of diltiazem tablets, and diltiazem SR capsules involving over 3300 patients, the most common adverse reactions were headache (4.6%), edema (4.6%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.5%), nausea (1.4%), rash (1.2%), and dyspepsia (1.0%).

In addition, the following events were reported with a frequency of less than 1.0%.

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

Nervous System: Amnesia, depression, gait abnormality, nervousness, somnolence, hallucinations, paresthesia, personality change, tinnitus, tremor, abnormal dreams, insomnia.

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

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

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

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, detached retina, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. 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, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and TEVA-DILTIAZEM therapy is yet to be established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been reports of diltiazem overdose in amounts ranging from < 1 g to 18 g. In cases with a fatal outcome, the majority involved multiple drug ingestion.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favourably 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 addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and intravenous calcium.

The effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases intravenous calcium has been administered (1 g calcium chloride or 3 g calcium gluconate) over 5 minutes, and repeated every 10-20 minutes as necessary. Calcium gluconate has also been administrated as a continous infusion at a rate of 2 g per hour for 10 hours: Infusions of calcium for 24 hours or more may be required. Patients should be monitored for signs of hypercalcemia.

In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination. The following measures may be considered:

Bradycardia

Administer atropine. If there is no response to vagal blockade, administer isoproterenol cautiously.

High Degree AV Block

Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing.

Cardiac Failure

Administer inotropic agents (isoproterenol, dopamine or dobutamine) and diuretics.

Hypotension

Vasopressors (e.g., dopamine or levarterenol bitartrate). Actual treatment and dosage should depend on the severity of the clinical situation.

DOSAGE AND ADMINISTRATION

Angina:

Chronic Stable Angina or Vasospastic Angina

Dosage must be adjusted to each patient's needs. Starting with 30 mg 4 times daily, before meals and at bedtime, dosage may be increased gradually to 240 mg a day (given in 3-4 equally divided doses) at one to two day intervals, until optimum response is obtained. Limited clinical experience in rare resistant cases suggests that dosage of up to 360 mg a day in 3-4 equally divided doses may be tried under careful supervision.

In patients with vasospastic angina, the last dose of the day may be given at bedtime to help minimize angina pain which in such patients frequently occurs in early morning.

Unstable Angina Pectoris

Dosage of TEVA-DILTIAZEM {diltiazem hydrochloride} tablets should be carefully titrated in the Intensive Care Unit, up to 360 mg/day given in 3-4 equally divided doses. The titration should be done as rapidly as possible with consideration of concomitant therapy {See PRECAUTIONS - Drug Interactions}.

Use in the Elderly

Pharmacokinetics of diltiazem in elderly patients has not been fully elucidated. Preliminary results in elderly patients (over 65 years old) suggest that a lower dosage might be required in this age group. {see PRECAUTIONS}.

There are few available data concerning dosage requirements in patients with impaired renal or hepatic function. If diltiazem must be used in these patients, the dosage should be carefully and gradually adjusted depending on patient tolerance and response {see PRECAUTIONS}.

TEVA-DILTIAZEM tablets should not be chewed or crushed.

AVAILABILITY OF DOSAGE FORMS

TEVA-DILTIAZEM, 30 mg: green coloured, round bi-convex film coated tablets, engraved novo on one side and 30 on the reverse contains 30 mg diltiazem hydrochloride. Supplied in bottles of 100 and in boxes of 100 tablets as unit dose strips.

TEVA-DILTIAZEM, 60 mg: light yellow coloured round bi-convex clear film coated tablets, engraved novo on one side and plain on the reverse contains 60 mg diltiazem hydrochloride.

60

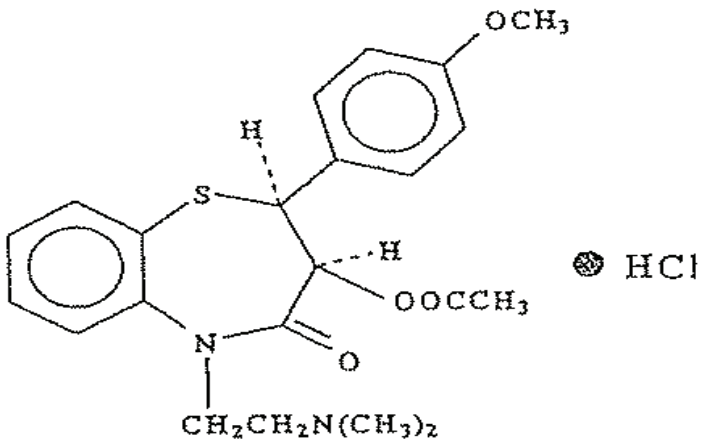
Supplied in bottles of 100 and in boxes of 100 tablets as unit dose strips.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5Hlone, 3-(acetyloxy)-5-[2(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+ l-cis-.

Chemical Structure:



Empirical Formula: $C_{22}H_{26}N_2O_4S \cdot HCl$ **Molecular Weight:** 450.98

Description: The compound is a white crystalline substance or powder having a bitter taste. Diltiazem is considered freely soluble in water, methanol or chloroform, slightly soluble in absolute ethanol and barely soluble in benzene.

COMPOSITION: Each TEVA-DILTIAZEM (diltiazem hydrochloride) tablet contains: lactose monohydrate, methocel K4M premium, colloidal silicon dioxide, magnesium stearate.

Each green 30mg tablet also contains: D&C Yellow #10 Lake 15% - 20%, FD&C Blue#1 Lake 11% - 13%, Opadry Clear YS-3-7413

Each light yellow 60mg tablet also contains: D&C Yellow #10 Lake 15% - 20%, FD&C Yellow#6 Lake 15% - 18%, Opadry Clear YS-3-7413

STORAGE RECOMMENDATIONS:

Keep between 15°C and 30°C. Blister packs should be stored between 15°C and 25°C and protected from high humidity.

PHARMACOLOGY

In Vitro Observations

Initial experimental work revealed that diltiazem was a coronary and peripheral vasodilator. Subsequent work substantiated that diltiazem's smooth muscle relaxant effect, as well as negative inotropic effect, resulted from the drug's ability to block excitation-contraction coupling by inhibiting slow calcium channel conduction. In a muscle bath study with isolated human coronary artery segments obtained at the time of cardiac transplantation, diltiazem produced nearly complete relaxation of potassium-contracted segments.

Studies in various experimental models have confirmed the negative inotropic effect of diltiazem. At low doses (1.1×10^{-7}M) diltiazem caused a reduction in contractile force of guinea pig papillary muscle with no demonstrable effect on the action potential. However, at higher concentrations (1.1×10^{-5}M) both a decrease in contractile tension and a lowering of maximum dp/dt were seen.

Studies done in isolated perfused rat hearts showed that diltiazem (10^{-6}M) decreases contractility without affecting action potential duration or resting membrane potential. In several experimental models it has been shown that the concentration of diltiazem required to produce smooth muscle relaxation and vasodilation is significantly less than the concentration required to produce a negative inotropic effect.

In Vivo Observations

Experiments in both open and closed chest dog models indicate that diltiazem increases coronary blood flow and reduces coronary vascular resistance. Intravenous diltiazem (100 μg/kg) increased coronary blood flow by 90%, with a predominant effect on large coronary arteries and collaterals. Increase in coronary blood flow has also been shown following diltiazem administration in both the epicardial and subendocardial regions in ischemic and non ischemic models. There was also a dose-related decrease in mean aortic pressure and systemic vascular

resistance with an increase in stroke volume and cardiac output. No significant change was noted in determinants of LV function such as LVEDP or LV dP/dT. The reduction in blood pressure that is seen with diltiazem is due to a direct vasodilatory effect on the blood vessels and is not mediated by sympathetic alpha receptor blockade, beta receptor stimulation, or ganglionic blockade. Diltiazem has been shown to inhibit the pressor responses induced by norepinephrine and angiotensin II.

In animal studies, the negative inotropic effect of diltiazem appears to be offset by its ability to decrease afterload and induce a mild reflex adrenergic response.

TOXICOLOGY

Acute Toxicity

Route	Animal	Sex	LD_{50} (mg/kg)	LD50 95% Confidence Limits (mg/kg)
Oral	mice	M & F	415 – 700	(343 – 736)
	rats	M & F	560 – 810	(505 – 1004)
s.c.	mice	M & F	260 – 550	(220 – 672)
i.p.	mice	M & F	187	(165 – 211)
	rats	M & F	211	(155 – 287)
i.v.	mice	M & F	58 – 61	(52 – 69)
	rats	M & F	38 - 39	(34 – 44)

Toxic effects appeared rapidly and toxicity included reduction of spontaneous activity, ptosis, piloerection, ataxia, loss of muscle tone and loss of righting reflex. Gross autopsy of animals who died as well as the survivors revealed no abnormalities.

Tolerance was evaluated in rabbits and dogs. Dogs received oral doses of 12.5, 25, 50 or 100 mg/kg. Ataxia, disorientation, decreased activity, diuresis and mydriasis were noted at 25 mg/kg. In addition, heavy sedation and emesis were seen at 50 mg/kg. At 100 mg/kg, convulsions occurred and one of the two animals died. Rabbits received 100, 200, 300, 400 mg/kg. The major symptoms were decreased activity, increased respiration, salivation and opisthotonos. One of the two rabbits died at 300 mg/kg and the two rabbits in the 400 mg/kg group died.

Subacute Toxicity

In rats, oral doses of 10, 20, 50, 100, 250 or 500 mg/kg/day of diltiazem were administered for 28 or 30 days. The relative liver weights of animals receiving 250 mg/kg/day and 500 mg/kg/day were increased. Microscopic examination revealed drug related degeneration of hepatic and renal cells in the highest dose group.

When the drug was given to rats intraperitoneally at 25 mg/kg/day for 30 days, hepatic and renal cell degeneration was seen. Macular hyaloid degeneration of the heart also was seen in 50% of the rats in this study.

Thirty day subacute studies in dogs revealed hepatic and renal cell degeneration when diltiazem was given at doses of 25 mg/kg/day orally and 5 mg/kg/day intravenously. Two dogs out of 5 receiving 50 mg/kg/day orally, died.

Chronic Toxicity/Carcinogenicity

In mice, diltiazem was administered at doses of 5, 15 or 30 mg/kg/day for a period of 21 months in females. Because of a lower survival, males were terminated at 20 months. Gross and histopathological examination failed to reveal any treatment related increase in the incidence of either neoplastic or other toxic lesions.

Rats received 6.25, 25 or 100 mg/kg/day of diltiazem for 24 months. An additional group received 200 mg/kg for 12 months. Treatment was terminated at 23 months in females receiving 100 mg/kg because of the low survival. Females had increased weight gain at 100 and 200 mg/kg, food consumption was increased among both sexes at these dose levels. Organ weight data revealed a significant increase in liver weight for rats of both sexes given 200 mg/kg. Microscopic evaluation revealed some evidence of dose dependent hepatic cytoplasmic vacuolization in rats treated with doses of 100 and 200 mg/kg/day and killed at 12 months. At 24

months, there were similar findings in control and treated animals. There was no increase in the incidence of neoplastic or other toxic lesions in rats treated with diltiazem.

Diltiazem was administered orally to dogs for 12 months at doses of 5, 10, 20 mg/kg/day. A dose related suppression of body weight gain became noticeable after 6 months.

Mutagenicity

No mutagenic changes were observed in the recombination test and two Ames reverse mutagenicity assays.

Reproduction Studies

Results in mice:

Route	Doses mg/kg	Time of administration during gestation	Findings in the Off spring
oral	10, 25, 50, 100, 200, 400	Day 7 to day 12	High incidence of vertebral column malformations when more than 50 mg/kg was administered
oral	Single doses of 12.5, 25, 50, 100, 200	One of days 7 to 14	Cleft palate and malformation of extremities or trunk were significantly higher when 50 or 100 mg/kg was administered on day 12. Vertebral malformations were most prevalent when 50 or 100 mg/kg was administered on day 9.
intra-peritoneal	0.2, 3.1, 6.3, 12.5, 25	Day 7 to day 12	Fetal mortality greatly increased when 12.5 mg/kg or more was administered. No teratogenic effect was demonstrated.
intra-peritoneal	Single dose of 3.1, 6.3, 12.5, 25, 50	One of days 5 to 16	Brachydactyly and hematoma in the extremities when 50 mg/kg was administered on day 13. Vertebral column malformations from the

			thoracic to coccygeal level of malformations of the ribs were observed when a dose of 25 mg/kg or greater was administered on day 9.

Results in rats:

Route	Doses mg/kg	Time of administration during gestation	Findings in the Off spring
oral	10, 50, 100, 200, 400	Day 9 to day 14	No teratogenic effect. High fetal death rate when 200 and 400 mg/kg was administered.
oral	10, 30, 100	Day 6 to 15	No teratogenic effect.
oral	Single dose of 300, 400, 600	On one of days 9 to 14	Significant incidence of skeletal malformations involving vertebrae and sternebrae when 400 mg/kg was administered on day 11. General edema, short of absent tail was observed when 600 mg/kg was administered on day 12.
intra-peritoneal	0.2, 2.0, 20, 40, 80	Day 9 to 14	Brachydactyly and hematoma in the front paw and tail and a high fetal mortality rate were observed when 80 mg/kg was administered.
intra-peritoneal	80	Day 9 to 11	Vertebral anomalies.
intra-peritoneal	80	Day 12 to 14	Brachydactyly, hematoma of the front paw and tail deformities and high fetal mortality rate.
intra-peritoneal	Single dose of 80	One of days 9 to 14	Fetal mortality increased on day 11 reached 100% on day 12 and decreased thereafter. Limb and tail deformities were induced when 80 mg/kg was administered on day 13 and 14. Vertebral column deformities were induced when 80 mg/kg was administered on day 11.
	Single dose of 40	One of days 11 to 14	No teratogenic effect.

Results in Rabbits:

Route	Doses mg/kg	Time of administration during gestation	Findings in the Off spring
oral	17.5, 35, 70	Day 6 to 18	Significant increase in skeletal malformations occurred when 35 mg/kg was administered. All pregnant dams aborted between days 21 and 25 of gestation when 70 mg/kg was administered.
intra-peritoneal	6.3, 12.5, 25	Day 7 to 16	Fetal mortality greatly increased at 12.5 mg/kg and reached 100% at 25 mg/kg. Skeletal defects and external malformations were induced when 12.5 mg/kg was administered. Their incidence was not statistically significant due to the low number of survivinq fetuses.

In fertility studies female rats received doses of 12.5, 25, 50 and 100 mg/kg p.o. In the 100 mg/kg group there was a reduction in the number showing a positive mating. However, the overall pregnancy rates and the average pre-coital time were comparable.

In peri-and post-natal studies, rats received diltiazem in doses of 10, 30 or 100 mg/kg/day from day 14 of gestation through day 21 post partum. Diltiazem was associated with a reduction in early individual weights and survival rates of the pups. At 100 mg/kg/day dystocia was evident. Retinal and tongue malformations were more frequent in the offspring of the 30 and 100 mg/kg/day group.

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