Pfizer

ڈِلـــزم

Dilzem®

(Diltiazem HCl)

DESCRIPTION

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

Mechanism of Action:
Although precise mechanisms of its anti-anginal actions are still being delineated, diltiazem is believed to act in the following ways:

Angina Due to Coronary Artery Spasm: Diltiazem has been shown to be a potent dilator of both epicardial and subendocardial coronary arteries. Spontaneous and ergonovine-induced coronary artery spasm are inhibited.

Exertional Angina: Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

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

THERAPEUTIC INDICATIONS

1. Unstable Angina Pectoris including Angina Due to Coronary Artery Spasm, or Following Myocardial Infarction: Dilzem® is indicated in the treatment of angina pectoris due to coronary artery spasm. Dilzem® has been shown to be effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).

2. Chronic Stable Angina (Classic Effort-Associated Angina): Dilzem® is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

3. Hypertension: Dilzem® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications, such as diuretics.

4. Kidney Transplantation: Dilzem® is indicated for the prevention of graft failure following kidney transplantation. Dilzem® is indicated for the reduction of cyclosporine-A nephrotoxicity during immunosuppressive therapy after kidney transplantation.

POSOLOGY AND METHOD OF ADMINISTRATION

Ischemic Heart Disease: (Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm): The initial dose is 120 mg/day in equally divided doses, administered preferably before meals, and at bedtime; dosage should be increased gradually in equally divided doses (two to four times daily) at one to two day intervals until optimum response is obtained. The optimum dosage range appears to be 180 to 360 mg/day. Doses up to 480 mg/day may be administered in some cases.

Hypertension: Dosages must be adjusted to each patient's needs.

The initial dose is 120-240 mg/day in equally divided doses, administered preferably before meals, and at bedtime. Maximum antihypertensive effect is usually observed at 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range is 240 to 360 mg/day.

There is an additive antihypertensive effect when Dilzem® is used with other antihypertensive agents. Therefore, the dosage of Dilzem® or the concomitant antihypertensive(s) may need to be adjusted when adding one to the other.

Kidney Transplantation: The initial dose is 120 mg/day in two equally divided doses. Depending on the patient's blood pressure, dosage may be increased up to a maximum of 360 mg/day given in 3 equally divided doses. The optimum dosage range appears to be 180 to 360 mg/day.

Concomitant Use with other Cardiovascular Agents
Nitroglycerin Therapy: Sublingual NTG may be taken as required to abort acute anginal attacks during Dilzem® hydrochloride therapy.

Prophylactic Nitrate Therapy: Although there have been no controlled studies to evaluate the anti-anginal effectiveness of this combination, Dilzem® may be co-administered with short- and long-acting nitrates.

SPECIAL POPULATIONS
Use in Renal Impairment: There are no available data concerning dosage requirements in patients with impaired renal function. If the drug must be used in such patients, titration should be done cautiously.

Use in Hepatic Impairment: There are no available data concerning dosage requirements in patients with impaired hepatic function. If the drug must be used in such patients, titration should be done cautiously.

Use in Children: Safety and effectiveness in children have not been established.

CONTRAINDICATIONS

Diltiazem is contraindicated in patients:

- with hypersensitivity to any component of this medication,
- with sick sinus syndrome except in the presence of a functioning ventricular pacemaker,
- with second or third-degree AV block except in the presence of a functioning ventricular pacemaker,
- with hypotension (less than 90 mm Hg systolic),
- with acute myocardial infarction,
- with pulmonary congestion documented by x-ray on admission,

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiac Conduction: Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction (see **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).
Experience with diltiazem used alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.

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

Acute Hepatic Injury: In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy.

Laboratory Monitoring: Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

General: Dermatological events may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiform and/or exfoliative dermatitis (epidermal necrolysis) have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued. (see Undesirable Effects).

The drug should be used with caution in patients with impaired renal or hepatic function.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Due to the potential for additive effects, caution and careful titration are warranted in patients concomitantly receiving any agent(s) known to affect cardiac contractility and/or conduction.

Diltiazem undergoes biotransformation by cytochrome P-450 (CYP) 3A4, mixed function oxidase. Diltiazem may competitively inhibit the metabolism of concomitant drugs which undergo the same route of biotransformation, thus increasing their plasma concentration. The extent of interaction and potentiation of effects depends on the variability of effect on (CYP) 3A4.

Beta-Blockers: There are few controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

Administration of diltiazem hydrochloride concomitantly with propranolol in normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment of the propranolol dose may be warranted (see **Special Warnings and Special Precautions for Use**).

H_2 antagonists: A study in healthy volunteers

has shown a significant increase in peak diltiazem plasma levels (58%) and in AUC (53%) after a one-week course of cimetidine at 1200 mg/day and diltiazem 60 mg/day. Ranitidine produced smaller, nonsignificant increases. Patients 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.

Digitalis: Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization.

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 blockers should be titrated carefully.

Cyclosporine: In patients with renal transplant receiving both medications concomitantly, diltiazem increases the plasma level of cyclosporine by as much as 30%. Therefore, the dosage of cyclosporine must be reduced when administering diltiazem and cyclosporine concomitantly.

Carbamazepine: Concomitant use of diltiazem and carbamazepine may enhance the plasma levels of carbamazepine, and consequently the risk of toxicity.

Warfarin, Rifampin, Lithium: There have been reports in the literature of diltiazem interactions with warfarin, rifampin or lithium.

PREGNANCY AND LACTATION

Pregnancy: There are no adequate, well-controlled studies in pregnant women; therefore, diltiazem should be administered to pregnant women only if the potential benefit to the patient justifies any risk to the patient and fetus.

Lactation: Diltiazem is excreted in human breast milk. One report suggests that concentrations in breast milk may approximate serum levels. Therefore, alternative methods of infant feeding should be instituted.

Effects on ability to drive and use machines

The effect of diltiazem on the ability to drive or use machinery has not been systematically evaluated.

UNDESIRABLE EFFECTS

In studies carried out to date, serious adverse reactions with Dilzem® have been rare; however, it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In 900 patients with hypertension, the most common adverse events were:

MedDRA System Organ Class	Undesirable Effects
Nervous system disorders	headache (8%), dizziness* (6%)
Cardiac disorders	atrioventricular block first degree (3%), sinus bradycardia* (3%)
Vascular disorders	flushing (3%)
General disorders and administration site conditions	asthenia (5%), oedema* (9%)

*Only edema and perhaps bradycardia and dizziness were dose related.

The most common adverse events (> 1%) observed in clinical studies of over 2100 angina and hypertensive patients receiving diltiazem were:

MedDRA System Organ Class	Undesirable Effects
Nervous system disorders	headache (4.5%), dizziness (3.4%)
Cardiac disorders	atrioventricular block first degree (1.8%), bradycardia (1.5%)
Vascular disorders	flushing (1.7%)
Gastrointestinal disorders	nausea (1.6%)
Skin and subcutaneous tissue disorders	rash (1.5%)
Musculoskeletal, connective tissue and bone disorders	joint swelling
General disorders and administration site conditions	asthenia (2.8%), fatigue, oedema (5.4%)

Less common adverse events included the following:

MedDRA System Organ Class	Undesirable Effects
Metabolism and nutrition disorders	anorexia, hyperglycaemia
Psychiatric disorders	confusional state, depression, hallucination, insomnia, nervousness, personality change, sleep disorder
Nervous system disorders	amnesia, paresthesia, somnolence, syncope, tremor
Eye disorders Ear and labyrinth disorders	amblyopia, eye irritation tinnitus
Cardiac disorders	angina pectoris, arrhythmia, atrioventricular block, cardiac failure congestive, extra systoles, palpitations, sinus arrest, tachycardia
Vascular disorders	hypotension
Respiratory, thoracic, and mediastinal disorders	dyspnoea, epistaxis, nasal congestion
Gastrointestinal disorders	constipation, diarrhea, dyspepsia, vomiting,
Hepato-biliary disorders	granulomatous liver disease
Skin and subcutaneous tissue disorders	angioedema, erythema multiforme, petechiae, pruritus, photosensitivity reaction, stevens-johnson syndrome, toxic epidermal necrolysis, urticaria
Musculoskeletal, connective tissue and bone disorders	arthralgia, musculoskeletal pain, myalgia
Renal and urinary disorders	nocturia, polyuria
Reproductive system and breast disorders	gynaecomastia, sexual dysfunction
General disorders and administration site conditions	gait disturbance
Investigations	alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, weight increased (see section **Special Warnings and Special Precautions for Use**)

In post-marketing experience, the following additional undesirable effect(s) have been reported:

MedDRA System Organ Class	Undesirable Effects
Gastrointestinal disorders	gingival hyperplasia
Skin and subcutaneous tissue disorders	acute generalized exanthematous pustulosis

OVERDOSE

Over dosage experience with oral Dilzem® has been limited. Single oral doses of 300 mg have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive medical care should be employed in addition to gastric lavage.

The following measures may be considered.

- Bradycardia: Administer atropine (0.60 to 1.0 mg); if there is no response to vagal blockade, cautiously administer isoproterenol.
- 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: Administer vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation.

SHELF LIFE

24 Months

HOW SUPPLIED

- Dilzem® tablets 30 mg is available in blister strips of 3 x 10's.
- Dilzem® tablets 60 mg is available in blister strips of 3 x 10's.
- Dilzem® Retard tablets 90 mg is available in blister strips of 2 x 10's.
- Dilzem® SR tablets 180 mg is available in blister strips of 2 x 10's.

DOSAGE

Use as directed by the physician.

INSTRUCTIONS

Avoid exposure to heat & sunlight.
Store below 30°C.
Keep out of the reach of children.

CAUTION

To be sold on the prescription of a registered medical practitioner only.

خوراک:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو گرمی اور سورج کی روشنی سے بچائیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

تاکید: صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔

Pfizer
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Pfizer Pakistan Ltd.
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