DILZEM®
(Diltiazem hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

DILZEM®
DILZEM RETARD®
DILZEM SR®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: diltiazem hydrochloride.

The chemical name for diltiazem hydrochloride is 1, 5-benzothiazepin-4(5H) one, 3-(acetyloxy)-5-[2-(dimethylamino)-ethyl]-2-3-dihydro-2-(4-methoxyphenyl),-monohydrochloride, (+)-cis-.

Its empirical formula is $C_{22}H_{26}N_2O_4S$ HCl.

Tablets for oral administration contain diltiazem hydrochloride equivalent to 30 mg, 60 mg, 90 mg and 180 mg a of diltiazem hydrochloride.

3. PHARMACEUTICAL FORM

Tablets
Sustained-release tablets.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

1. Unstable Angina Pectoris including Angina Due to Coronary Artery Spasm, or Following Myocardial Infarction

Diltiazem is indicated for the treatment of angina pectoris due to coronary artery spasm. Diltiazem 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)

Diltiazem is indicated for 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[1]

Diltiazem 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[2,3,4,5,6,7,8]

Diltiazem is indicated for the prevention of graft failure following kidney transplantation. Diltiazem is indicated for the reduction of ciclosporin A nephrotoxicity during immunosuppressive therapy after kidney transplantation.

4.2. 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 1- to 2-day intervals until optimum response is obtained. The optimum dosage range appears to be 180 mg/day 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 mg/day to 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 mg/day to 360 mg/day.

There is an additive antihypertensive effect when diltiazem is used with other antihypertensive agents. Therefore, the dosage of diltiazem 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 three equally divided doses. The optimum dosage range appears to be 180 mg/day to 360 mg/day.

Concomitant Use With Other Cardiovascular Agents

Nitroglycerin Therapy

Sublingual nitroglycerin (NTG) may be taken as required to abort acute anginal attacks during diltiazem therapy.

Prophylactic Nitrate Therapy

Although there have been no controlled studies to evaluate the antianginal effectiveness of this combination, diltiazem 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.

4.3. 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.

4.4. 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 section **4.5. 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 either cardiac index or in 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 diltiazem therapy may occasionally result in symptomatic hypotension.

Acute Hepatic Injury

In rare instances, significant elevations in enzymes such as alkaline phosphatase, lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (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 the 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 multiforme and/or exfoliative dermatitis (epidermal necrolysis)[25] have also been infrequently reported. Should a dermatological reaction persist, the drug should be discontinued (see section **4.8. Undesirable Effects**).

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

4.5. 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 P450 3A4 (CYP3A4)[26] mixed function oxidase.[9] Diltiazem may competitively inhibit the metabolism of concomitant drugs that undergo the same route of biotransformation, thus increasing their plasma concentration.[26] The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4.

Ivabradine[33]

Diltiazem and ivabradine are both associated with a heart rate lowering effect. Furthermore, concomitant use of diltiazem with ivabradine increases exposure (C_{max}, AUC) of ivabradine due to CYP3A4 inhibition, which may result in an additional heart rate lowering effect. Therefore, their concurrent use is not recommended.

Beta-blockers[10]

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 section **4.4. special warnings and precautions for use**).

H_2 Antagonists[11]

A study in healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area under curve (AUC) (53%) after a 1-week course of cimetidine at 1200 mg/day and diltiazem 60 mg/day. Ranitidine produced smaller, non-significant 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[12]

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.

Ciclosporin

In patients with renal transplant receiving both medications concomitantly, diltiazem increases the plasma level of Ciclosporin by as much as 30%.[13,14] Therefore, the dosage of Ciclosporin 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.[15,16,17]

Statins

Diltiazem is an inhibitor of CYP3A4 and has been shown to increase significantly the AUC of some statins. The risk of myopathy and rhabdomyolysis with statins metabolized by CYP3A4 may be increased with concomitant use of diltiazem. When possible, use a non-CYP3A4-metabolized statin together with diltiazem; otherwise, dose adjustments for both diltiazem and the statin should be considered along with close monitoring for signs and symptoms of any statin related adverse events.[31]

Mechanistic Target of Rapamycin (mTOR) Inhibitors[34]

Sirolimus C_{max} and AUC were increased 1.4, and 1.6 fold, respectively following simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. Diltiazem may increase everolimus blood concentrations by decreasing metabolism via CYP3A4 or the efflux of everolimus from intestinal cells. In addition, sirolimus is a principal

metabolite of temsirolimus with an equally potency. A dose reduction of mTOR inhibitor such as sirolimus, temsirolimus, and everolimus, may be necessary if diltiazem is coadministered.

4.6. FERTILITY, 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.

4.7. 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.

4.8. UNDESIRABLE EFFECTS[29,32]

In studies carried out to date, serious adverse reactions with diltiazem 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 oedema 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	Amblyopia, eye irritation
Ear and labyrinth disorders	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 **4.4. special warnings and precautions for use**)

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

Frequency: Not known

MedDRA System Organ Class	Undesirable Effects
Gastrointestinal disorders	Gingival hyperplasia[27]
Nervous system disorders	Myoclonus[30], extrapyramidal disorder[32]
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis[28,35]

4.9. OVERDOSE

Overdosage experience with oral diltiazem 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 (0.60-1.0 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 (e.g., dopamine or levarterenol bitartrate).

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

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 antianginal 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.

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

Hemodynamic and Electrophysiologic Effects

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

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end-diastolic pressure have not been affected.[18,19] Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).[20,21]

Chronic oral administration in doses of up to 360 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation.

Diltiazem produces antihypertensive effects in both the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with chronic antihypertensive effects. Diltiazem 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 produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed.

5.2. PHARMACOKINETIC PROPERTIES

Absorption[22,23,24]

Diltiazem is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to IV dosing) of about 40%. Single oral doses of 30 mg to 120 mg result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 3 hours after drug administration. There is a departure from dose-linearity when single doses of diltiazem above 60 mg are given; a 120 mg dose gave plasma levels three times that of the 60 mg dose.

Distribution[22,23,24]

In vitro studies have shown that 70% to 80% of diltiazem is bound to plasma proteins. Competitive ligand binding studies also have shown that binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Therapeutic plasma levels of diltiazem appear to be in the range of 50 ng/mL to 200 ng/mL.

Metabolism[22,23,24]

Diltiazem undergoes extensive hepatic metabolism and undergoes biotransformation by cytochrome P-450 (CYP) 3A4;[26,33] therefore, only 2% to 4% of the unchanged drug appears in the urine. In cases of serious liver damage, delayed biotransformation may be anticipated. Desacetyldiltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilatory as diltiazem.

Excretion[22,23,24]

The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours.

5.3. PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Magnesium Stearate USP
Lactose K PH EUR
Stearic Acid Powdered DAC
Hydrogenated Castor Oil
Sodium Carboxymethyl Cellulose

6.2. INCOMPATIBILITIES

Not available.

6.3. SHELF LIFE

24 Months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at controlled room temperature 15°C to 30°C (59°F - 86°F).

Avoid exposure to heat, sunlight and moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

- DILZEM® tablets 30 mg is available in blister strips of 3 x 10s
- DILZEM® tablets 60 mg is available in blister strips of 3 x 10s
- DILZEM® RETARD tablets 90 mg is available in blister strips of 1 x 15s
- DILZEM® SR tablets 180 mg is available in blister strips of 1 x 15s

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Not available.

Dilzem/LPD/PK-06

According to CDS V 9.0 dated February 07, 2018; Supersedes CDS V 8.0 dated March 02, 2017

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