

New Zealand Data Sheet



1. PRODUCT NAME

Dilzem® 30 mg film coated tablets
Dilzem® 60 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diltiazem hydrochloride 30 mg
Diltiazem hydrochloride 60 mg

Excipient(s) with known effect:

Dilzem tablets contain lactose. For the full list of excipients, *see section 6.1.*

3. PHARMACEUTICAL FORM

Dilzem 30 mg tablet: a white, circular, film-coated, biconvex tablet of approximately 6mm diameter embossed "D" one side.

Dilzem 60 mg tablet: a white capsule shaped, film-coated tablet, 10mm in length and 5mm wide; with a breakline and 'DL60' engraved on one face.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Angina pectoris due to coronary artery spasm and chronic stable angina.

4.2. Dose and method of administration

Dose

Adults

Initially 30 mg three to four times daily increasing to 240 mg daily in divided doses. The maximum recommended dose is 360 mg daily.

Special populations

Elderly population

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 Section 4.4.*

Hepatic and renal impairment

Dilzem should be used with caution in patients with hepatic or renal impairment. If diltiazem must be used in these patients, the dosage should be carefully and gradually adjusted depending on patient tolerability and responses, *see Section 4.4.*

Concomitant use with other cardiovascular agents

Sublingual glyceryl trinitrate may be taken as required to abort acute anginal attacks during Dilzem therapy. Diltiazem may be safely co-administered with short- and long-acting nitrates but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Beta-blockers- *see Section 4.4.*

Antihypertensives- Diltiazem has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem or the concomitant antihypertensives may need to be adjusted when adding one to the other

Paediatric population

Safety and efficacy in children has not been established. Therefore, diltiazem is not recommended for use in children.

Method of Administration

Oral administration.

4.3. Contraindications

- Patients with sick-sinus syndrome except in the presence of a functioning ventricular pace-maker.
- Patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker.
- Patients with hypotension (< 90mmHg systolic).
- Severe congestive heart failure
- Severe bradycardia.
- Concomitant use of dantrolene infusion (see Section 4.5)
- Concomitant use of ivabradine
- Idiosyncrasy or hypersensitivity to diltiazem or any of the excipients listed under Section 6.1.
- Breastfeeding
- Left ventricular failure with pulmonary congestion.
- Patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.
- Pregnancy.

4.4. Special warnings and precautions for use

Mood Changes: Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression, *see Sections 4.5 and 4.8.*

Intestinal Motility: 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.

Cardiac Conduction: Closed 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 effect may rarely result in abnormally slow heart rates (particularly in patient with sick sinus syndrome or second or third degree AV block (six of 1,243 patients or 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction, *see Section 4.5.* A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, haemodynamic 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 the use of diltiazem alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the medicine in patients, *see Section 4.5.*

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

Acute Renal Failure: Cases of acute renal failure have been reported in patients using diltiazem at therapeutic dosages. Patients at greater risk appear to have reduced left ventricular function, severe bradycardia or severe hypotension.

Acute Hepatic Injury: In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, AST, ALT and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in most cases, but probable in some, *see Section 4.8.*

Dermatological Events: Dermatological events, *see Section 4.8,* may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported. Should dermatological reactions 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. Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

Respiratory Events: The use of diltiazem may induce bronchospasm, including asthma aggravation, especially in patients with pre-existing bronchial hyper-reactivity. Cases have also been reported after dose increase. Patients should be monitored for signs and symptoms of respiratory impairment during diltiazem therapy.

Concomitant Administration with Beta-Blockers: Controlled and uncontrolled studies suggest that concomitant use of diltiazem and beta- blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities, *see Section 4.5*. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted.

Use with Amiodarone: Amiodarone should be used with caution with diltiazem particularly if there is suspicion of underlying dysfunction of the sinus node such as bradycardia, sick sinus syndrome or if there is a partial AV block, *see Section 4.5*.

Concomitant Use with Digoxin: Diltiazem has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics, *see Section 4.5*. Patients with plasma digoxin levels in the upper therapeutic range (1.5 to 2.5 ng/mL) may develop toxic plasma concentrations and side effects. Therefore, digoxin plasma concentrations should be controlled 6 to 8 days after starting these drug combinations, at which time new steady state conditions develop and the digoxin dose can be reduced if there is evidence of toxicity.

Long Term Use: Data to support long-term use of diltiazem (longer than 1 year) with doses higher than 240 mg/day is limited. Therefore, the long-term treatment with doses exceeding 240 mg/day is not recommended.

Abrupt Withdrawal: The sudden withdrawal of diltiazem has been associated with severe angina.

Use in Hepatic or Renal Impairment: Increase of plasma concentrations of diltiazem may be observed in the elderly and in 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.

Diltiazem hydrochloride is extensively metabolised 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. Diltiazem should be used with caution in patients with renal or hepatic

impairment. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Use in the Elderly: Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. Plasma diltiazem concentrations can be increased in the elderly. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include peripheral oedema, bradycardia, palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable, *see Section 4.2*.

Paediatric Population: Safety and effectiveness in children have not been established. Therefore, diltiazem is not recommended for use in children.

Effects on Laboratory Tests: No data available.

4.5. Interaction with other medicines and other forms of interaction

Due to the potential for additive effects, caution and careful titration are necessary in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction.

Diltiazem is metabolised by CYP3A4. A moderate (less than 2-fold) increase of diltiazem plasma concentration in cases of co-administration with a stronger CYP3A4 inhibitor has been documented. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plasma concentration of either co-administered drug. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase.

Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition or induction of metabolism. This may lead to an increased risk of adverse reactions.

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.

Ciclosporin

Concomitant administration of diltiazem and ciclosporin has resulted in increased blood ciclosporin concentrations and consequent ciclosporin-induced nephrotoxicity. Although further study is needed, it has been suggested that diltiazem may interfere with metabolism of ciclosporin via hepatic microsomal enzyme inhibition. The possibility that diltiazem may increase serum ciclosporin concentrations should be considered if the drugs are used concomitantly. It is recommended that the ciclosporin dose be reduced, renal function be monitored, circulating ciclosporin levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.

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.

Corticosteroids (methylprednisolone)

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.

Benzodiazepines (midazolam, triazolam)

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.

Beta-blockers

Controlled and uncontrolled studies suggest that concomitant diltiazem and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

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

Due to the possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect), combination therapy with diltiazem and beta-blockers must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

An increased risk of depression has been reported when diltiazem is co-administered with beta-blockers, *see Section 4.8*.

Digoxin

Concomitant use of diltiazem and digoxin may result in additive effect on conduction. Diltiazem has been shown to modify digoxin pharmacokinetics in healthy subjects, in patients with cardiac insufficiency and in patients with chronic atrial fibrillation. Increases in plasma digoxin concentrations ranged from 24% to 70%. The renal digoxin clearance was decreased from 86.9 ± 18.3 to 62.8 ± 15.4 mL/minute and digoxin elimination half-life was prolonged from 36.7 ± 11.2 to 44.5 ± 11.5 hours during diltiazem coadministration. There is an increased risk of bradycardia with this combination. Caution is required when digoxin is combined with diltiazem, particularly in the elderly and when high doses are used.

H2 antagonists (cimetidine, ranitidine)

Concomitant use may result in increased plasma diltiazem concentrations. Patients receiving diltiazem concurrently with an H2 antagonist should be carefully monitored when initiating or discontinuing therapy with H2 antagonists. An adjustment in diltiazem daily dose may be necessary.

Concurrent administration of cimetidine produced an increase in single dose diltiazem levels (approximately 50% over control). The plasma levels of diltiazem's metabolite, desacetyldiltiazem were also increased.

Diazepam

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%.

Carbamazepine

Concomitant use may result in increased circulating carbamazepine levels. It is recommended that the plasma carbamazepine concentrations be assayed and that the dose should be adjusted if necessary.

Phenytoin

When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration. It is recommended that the phenytoin plasma concentrations be monitored.

Lithium

There is an increased risk of lithium-induced neurotoxicity.

Theophylline

Concomitant use results in an increase in circulating theophylline levels.

Ivabradine

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of 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.

Amiodarone

Sinus arrest and 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 on myocardial contractility, *see Section 4.4*. 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.

Short and long acting nitrates

Increased hypotensive effects and faintness may be seen due to additive vasodilating effects. In patients treated with calcium channel antagonists, the addition of nitrate derivatives should only be carried out at gradually increasing doses.

Anaesthetic agents

Additive haemodynamic depressive effects are found when calcium channel blockers are combined with inhalation anaesthetic agents such as halothane, isoflurane or enflurane. These effects are related both to the anaesthetic concentration and to the dose of the calcium channel blocker. Depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment.

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.

Administration of a single 20 mg dose of simvastatin in 10 healthy volunteers, after 2 weeks of 120 mg of Cardizem SR twice daily, resulted in a significantly ($p < 0.05$) increased mean peak serum concentration of simvastatin by 3.6 fold and simvastatin acid by 3.7 fold, the AUC by 4.8 fold for simvastatin and the elimination half-life by 2.3 fold. There was no change in the time to peak

concentration curve for simvastatin and simvastatin acid. Concomitant use of diltiazem with simvastatin should be used with caution, particularly at the higher end of the dosing range.

In another 10-volunteer study, the coadministration of 120 mg of Cardizem SR twice daily with lovastatin resulted in a 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone.

No change in pravastatin AUC and C_{max} was observed during Cardizem SR coadministration. The effects of statins on the pharmacokinetic parameters of diltiazem have not been determined.

Cilostazol

Concomitant administration has resulted in the inhibition of cilostazol metabolism (CYP3A4). Diltiazem has been shown to increase cilostazol exposure and to enhance its pharmacological activity.

Other antiarrhythmic agents

Since diltiazem has antiarrhythmic properties, its concomitant use with other antiarrhythmic agents is not recommended (additive risk of increased cardiac adverse effects). Such combination should only be used under close clinical and ECG monitoring.

Aspirin/Acetylsalicylates

The concomitant administration of aspirin/acetylsalicylates with diltiazem should be undertaken with caution because of the increased risk of bleeding due to potential additive effect on platelet aggregation.

Other Antiplatelet Drugs

In a pharmacodynamic study, diltiazem was shown to inhibit platelet aggregation. Although the clinical significance of this finding is unknown, potential additive effects when used with antiplatelet drugs should be considered.

Grapefruit Juice

Grapefruit juice may increase diltiazem exposure. Patients who consume grapefruit juice should be monitored for increased effects of diltiazem. Grapefruit juice should be avoided if an interaction is suspected.

X-ray Contrast Media

Cardiovascular effects of an intravenous bolus of an ionic X-ray contrast media, such as hypotension, may be increased in patients treated with diltiazem. Special caution is required in patients who concomitantly receive diltiazem and X-ray contrast media.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no well-controlled studies of the use of diltiazem HCl in pregnant women. Also, diltiazem is a calcium channel blocker and drugs listed in this class carry the potential for foetal hypoxia associated with maternal hypotension. Diltiazem is therefore not recommended during pregnancy, as well as in women of child-bearing potential not using effective contraception. See Section 5.3 for preclinical data.

Breast-feeding

Diltiazem levels were measured in both serum and milk in lactating women. Samples were taken simultaneously on the fourth day of the treatment with diltiazem 60 mg four times a day. The peak level in milk was as high as 200 ng/mL and was almost the same as that in serum. These data show that diltiazem is freely diffusible in milk but it is not known whether it is harmful to the newborn. Therefore, breastfeeding while taking this drug should be avoided. If use of diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness and malaise, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8. Undesirable effects

The following undesirable effects are ranked according to System Organ Class and to their frequencies. Frequencies are defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

| System organ class | Frequency and symptom |
|--------------------------------------|---|
| Metabolism and nutritional disorders | Uncommon: hyperglycaemia, hyperuricaemia |
| Nervous system disorders | Common: headache (2.1%), dizziness (1.5%), asthenia (1.2%), light-headedness Uncommon: abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality change, somnolence, tinnitus, tremor |
| Eye disorders | Uncommon: amblyopia, eye irritation |
| Cardiac disorders | Common: AV block (1.6%), can be first, second or third degree (see Section 4.4) and palpitations |

| System organ class | Frequency and symptom |
|--|--|
| | Uncommon: angina, arrhythmia, bradycardia, bundle branch block, congestive heart failure, ECG abnormality, hypotension, syncope, tachycardia, ventricular extrasystoles |
| Vascular disorders | Common: flushing Uncommon: orthostatic hypotension |
| Respiratory disorders | Uncommon: dyspnoea |
| Gastrointestinal disorders | Common: nausea (1.9%), constipation, dyspepsia, gastric pain Uncommon: anorexia, diarrhoea, dry mouth, dysgeusia, thirst, vomiting, weight increase |
| Hepato-biliary disorders | Uncommon: hepatic enzymes increase (AST, ALT, LDH, ALP), (in rare cases, clinical hepatitis has been reported, reversible upon discontinuation of diltiazem; see Section 4.4) |
| Skin and subcutaneous tissue disorders | Common: rash (1.3%), erythema Uncommon: Petechiae, photosensitivity, pruritus Rare: urticaria |
| Musculoskeletal and connective tissue disorders | Uncommon: CPK increase, muscle cramp, osteoarticular pain |
| Renal and urinary disorders | Uncommon: nocturia, polyuria |
| Reproductive system and breast disorders | Uncommon: impotence, sexual difficulties |
| General disorders and administration site conditions | Very common: lower limb oedema Common: oedema (2.4%), malaise Uncommon: epistaxis, nasal congestion |

Post-marketing experience

The following post-marketing events have been reported infrequently in patients receiving diltiazem: mood changes including depression, hyperglycaemia, extrapyramidal syndrome, sino-atrial block, congestive heart failure, sinus arrest, cardiac arrest (asystole), photosensitivity, hepatitis, alopecia, gynaecomastia, vasculitis, musculo-cutaneous reactions such as simple erythema or occasionally desquamative erythema with or without fever, angioneurotic oedema, symptoms of vasodilation (such as flushing, lower limb oedema, sweating), erythema multiforme (including rare cases of Steven-Johnson's syndrome), exfoliative dermatitis, acute generalised exanthematous pustular dermatitis or pustulosis, orthostatic hypotension, malaise, gastric pain, extrapyramidal symptoms, gingival hyperplasia, haemolytic anaemia, 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 rash, characterised as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy cannot yet be established. Bronchospasm (including asthma aggravation) has also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

The oral LD₅₀ in mice and rats ranged from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD₅₀ in these species was 60 and 38 mg/kg, respectively. The oral LD₅₀ in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is 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 involved with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Symptoms

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse and acute kidney injury, sinus bradycardia with or without isorhythmic dissociation, sinus arrest, cardiac arrest, heart block, cardiac failure, and atrio-ventricular conduction disturbances. 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 utilised 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/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

Treatment

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or haemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia:

Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoprenaline 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 (isoprenaline, dopamine, or dobutamine) and diuretics;

Hypotension:

Vasopressors (e.g., dopamine or noradrenaline acid tartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blocker, Benzothiazepine derivatives; ATC code: C08D B01

Mechanism of action

Although precise mechanisms of its antianginal actions are still being delineated, diltiazem is believed to act in the following ways:

1. Vasospastic angina: Diltiazem has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergometrine induced coronary artery spasm are inhibited by diltiazem.
2. Exertional angina: Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand and increase oxygen supply. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise workloads and by dilating coronary arteries.

In animal models, diltiazem interferes with the slow inward (depolarising) 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 which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and sub-endocardial) occur in ischaemic and nonischaemic models and are accompanied by dose dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Haemodynamic and Electrophysiologic Effects

Like some other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular 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 ergometrine 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 ischaemic heart disease, reduces the heart rate/blood pressure product for any given workload. 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. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first degree AV block. 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).

Chronic oral administration of diltiazem in doses of up to 240 mg/day has resulted in small increases in PR interval but has not usually produced abnormal prolongation. There were, however, three instances of second degree AV block and one instance of third degree AV block in a group of 959 chronically treated patients.

5.2. Pharmacokinetic properties

Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of diltiazem result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. 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 vasodilator as diltiazem. Therapeutic blood levels of diltiazem appear to be in the range of 50 to 200 ng/mL. There is a departure from dose linearity when single doses above 60 mg are given; a 120 mg dose gave blood levels three times that of the 60 mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

5.3. Preclinical safety data

Reproduction studies have been conducted in mice, rats and rabbits. Administration of high doses has resulted in embryo and foetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the prenatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at high doses.

Further relevant information is included in the other sections of the Data Sheet.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dilzem tablets contain the following excipients:

Lactose, Cutina HR, Aluminium hydroxide gel dried, Eudragit NE30D, Talc, and Magnesium stearate for the core and Opadry white (Y-IR-7000B) for coating.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

Bottles of 100, 500 or 1,000 tablets.

Blister packs of 30 tablets.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

Dilzem 30 mg: 10 April 1989
Dilzem 60 mg: 27 November 1986

10. DATE OF REVISION OF THE TEXT

17 June 2020

Summary table of changes

| Section Changed | Summary of new information |
|-----------------|--|
| 4.2 | Concomitant use with antihypertensives- added section |
| 4.3 | Added breastfeeding |
| 4.4 | Added Acute Renal Failure, Dermatological Events, Use in Hepatic or Renal Impairment and Use in the Elderly sections. Added new information to Cardiac Conduction, Congestive Heart Failure, Use in Diabetes and Concomitant Use of Digoxin. |
| 4.5 | Added new sections: Dantrolene infusion, Rifampicin, Corticosteroids, Phenytoin, Lithium, Ivabradine, Alpha Blockers, Amiodarone, Anaesthetic Agents, Cilostazole, Aspirin, X-ray Contrast Media. |
| 4.6 | Added new information to Breast-feeding section |
| 4.7 | Fatigue changed to malaise |
| 4.8 | New undesirable effects table |
| 4.9 | New measures are added for Bradycardia, High Degree AV Block, Cardiac Failure and Hypotension. |
| 5.1 | Mechanism of Action section updated; new section added Haemodynamic and Electrophysiologic Effects |
| 5.2 | Pharmacokinetic Properties section revised. |
| 5.3 | Added new information- animal reproductive studies data |