NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Cardizem 60 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diltiazem hydrochloride 60 mg

Chemically, diltiazem hydrochloride is the hydrochloride salt of (2S, 3S)-5-(2-dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate.

Excipients with known effect: lactose monohydrate and methyl hydroxybenzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cardizem 60 mg tablets are clear coated, light yellow, round double (13/32" or 1.03 cm) convex tablets with characteristic direct compression speckle. The word "Marion" is engraved on one side while the other side is scored and engraved with 1772.

Cardizem contains a white to off-white crystalline powder with a bitter taste. It is freely soluble in water, methanol, and chloroform.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Patients with moderate to severe angina pectoris due to atherosclerotic coronary artery disease or coronary artery spasm (vasospastic angina).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Angina

Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one to two day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. The maximum recommended dose is 360 mg daily. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

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 Section 4.4).

Use in patients with renal or hepatic impairment

Diltiazem should be used with caution in patients with renal or hepatic impairment (see Section 4.4).

CONCOMITANT USE WITH OTHER ANTIANGINAL AND ANTIHYPERTENSIVE AGENTS

Sublingual glyceryl trinitrate may be taken as required to abort acute anginal attacks during 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 aged has not been established. Therefore, diltiazem is not recommended for use in children.

Method of administration

For oral administration

4.3 CONTRAINDICATIONS

- Sick sinus syndrome except in the presence of a functioning ventricular pacemaker
- Second or third degree AV block except in the presence of a functioning ventricular pacemaker
- Hypotension (less than 90 mmHg systolic)
- Severe congestive heart failure
- Severe bradycardia (below 40 bpm)
- Concomitant use of dantrolene infusion (see Section 4.5)
- Concomitant use of ivabradine (see Section 4.5)
- 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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression (see Section 4.5 and Section 4.8).

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

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with a first degree AV block detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients 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 drug in such 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 or sick sinus syndrome or if there is partial AV block (see Section 4.5).

Concomitant Use of 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.

H_2 antagonists (cimetidine, ranitidine)

Concomitant use may result in increased plasma diltiazem concentrations. Patients receiving diltiazem concurrently with an H_2 antagonist should be carefully monitored when initiating or discontinuing therapy with H_2 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 (see Section 4.3).

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 vasodilatating 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 (Category C)

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.

There are no well controlled studies 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.

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

On the basis of reported adverse drug reactions, i.e. dizziness (common), malaise (common), the ability to drive and use machines could be altered. However, no studies have been performed.

4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been reported. They are presented in the following table by system organ class (SOC) and ranked under heading of frequency.

The following CIOMS frequency rating is used:

Very common: ≥10%; Common: ≥1 and <10%; Uncommon: ≥0.1 and <1%; Rare: ≥0.01 and <0.1%; Very rare: <0.01%; Not known: cannot be estimated from 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%), lightheadedness
	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
	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 adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

The oral LD_{50} in mice and rats ranged from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50} in these species was 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. 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.

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.

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

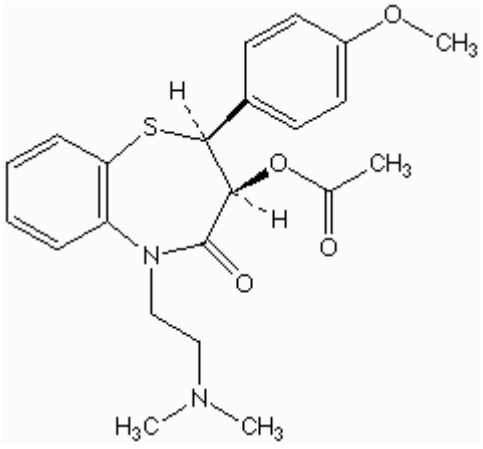
Vasopressors (eg, dopamine or noradrenaline acid tartrate).

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

Diltiazem hydrochloride (CAS 33286-22-5) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Its molecular formula is $C_{22}H_{26}N_2O_4S.HCl$ and it has the following structure:



•HCl

It has a molecular weight of 450.98.

5.1 PHARMACODYNAMIC PROPERTIES

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

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

Mechanisms 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 work loads 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

No further relevant information other than that which is already included in the other sections of the Data Sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cardizem tablets contain lactose monohydrate, microcrystalline cellulose, hypromellose, colloidal anhydrous silica, magnesium stearate, methyl hydroxy benzoate, colouring (Quinoline Yellow CI 47005 & Sunset Yellow FCF CI 15985) and a film coating (Opadry YS-5-7044 and methyl hydroxy benzoate).

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

Cardizem 60 mg in bottle size of 7* has a shelf life of 36 months from date of manufacture.

Cardizem 60 mg in bottles of 90* and 100* has a shelf life of 48 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light and moisture. Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Cardizem 60 mg tablets are supplied in plastic high density polyethylene bottles of 7*, 90* or 100* tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

sanofi-aventis new zealand ltd
Level 8, 56 Cawley Street, Ellerslie
Auckland New Zealand
Toll Free Number (medical information): 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

19 July 1984

10 DATE OF REVISION OF THE TEXT

20 April 2020

*Denotes presentations not available in New Zealand

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Acute renal failure warning added
4.9	Update to section to include acute kidney injury