

AUSTRALIAN PRODUCT INFORMATION DILTIAZEM SANDOZ® CD (DILTIAZEM HYDROCHLORIDE)

1 NAME OF THE MEDICINE

Diltiazem hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diltiazem Sandoz CD capsules contain a blend of beads with controlled dissolution characteristics for once-a-day administration. The capsules are available as either 180 mg, 240 mg or 360 mg diltiazem hydrochloride in sustained release form.

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

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Modified release capsule

Diltiazem Sandoz CD is registered in 3 strengths:

180 mg: Light turquoise blue/blue capsule

240 mg: Blue/blue capsule

360 mg: Light blue/white capsule

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Diltiazem Sandoz CD is indicated for the treatment of hypertension.

Diltiazem Sandoz CD is also indicated for the management of chronic stable angina (effort-associated angina) where there is no evidence of vasospastic or unstable angina. Since the safety and efficacy of CD capsules in the management of unstable or vasospastic angina has not been substantiated, use of this formulation for these indications is not recommended.

4.2 DOSE AND METHOD OF ADMINISTRATION

For oral administration.

Patients controlled on diltiazem alone or in combination with other medications may be safely switched to Diltiazem Sandoz CD at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited clinical experience with doses above 360 mg. Therefore, treatment with doses exceeding 360 mg/day is not recommended.

Hypertension

Dosage needs to be adjusted by titration to individual patient needs. Monitoring of trough BP should be done initially to ensure BP control lasts over dosing period. When used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg daily.

Angina

Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 180 mg once daily. Individual patients may respond to higher doses of up to 360 mg once daily. When necessary, titration may be carried out over a 7 to 14 day period.

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).

Impaired hepatic or renal function

There are few available data concerning dosage requirements in patients with impaired renal or hepatic function. Diltiazem should be used with caution in patients with renal or hepatic 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 diltiazem therapy. Diltiazem may be safely coadministered with short- and long-acting nitrates.

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.

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)
- 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
- 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 (nine of 2,111 patients, or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction (see also 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 hydrochloride.

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). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction $24\% \pm 6\%$) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination (see also Section 4.5).

Hypotension

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

Acute Hepatic Injury

Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. 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 tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some 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 also been infrequently reported. Should a dermatological reaction 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 also Section 4.5).

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

In contrast, there appears to be no effect on the pharmacokinetics of atenolol, a renally cleared drug. In view of the known pharmacodynamic interactions between these classes of drugs, this effect may be of clinical relevance.

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 A-V block (see also Section 4.5).

Concomitant Use of Digoxin

Diltiazem has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics (see also 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 or with doses higher than 360 mg/day are limited. Treatment at doses above 360 mg/day does not offer increased efficacy, but is associated with a greater risk of adverse reactions. Therefore treatment with doses exceeding 360 mg/day is not recommended.

Abrupt Withdrawal

The sudden withdrawal of diltiazem has been associated with severe angina in anginal patients.

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 is extensively metabolised by the liver and excreted by the kidneys and in bile. As with any new 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 studies 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 Use

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

No pharmacokinetic interaction studies have been conducted with the Diltiazem Sandoz CD or SR formulations. However, interactions reported with the conventional formulation are still relevant. As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration 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.

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.

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.

Beta-blockers

Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers or digitalis 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.

Administration of diltiazem concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased by 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 an 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 conventional 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 desacetyl diltiazem 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 a 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 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 diltiazem 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 diltiazem 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 diltiazem 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

Effects on Fertility

No data available.

Use in 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.

Use in Lactation

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Serious adverse reactions have been rare in studies carried out to date, but it should be recognised that patients with impaired ventricular function and cardiac conduction abnormalities have been usually excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving diltiazem CD up to 360 mg with rates in placebo patients shown for comparison.

**Table 1 - DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION AND ANGINA TRIALS
(with the CD formulation)**

ADVERSE REACTION	diltiazem CD	PLACEBO
	N=607	N=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV block first degree	3.3%	--
Oedema	2.6%	1.3%
ECG abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of diltiazem as CD capsules, tablets and SR capsules involving 3,200 patients, the most common events (i.e. greater than 1%) were oedema (4.6%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), dyspepsia (1.2%), palpitations, lower limb oedema, malaise, constipation, gastric pain and erythema.

Lower limb oedema has been reported as very common.

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular

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

Nervous system

Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal

Anorexia, constipation, diarrhoea, dry mouth, dysgeusia, dyspepsia, hepatic enzymes increase (AST, ALT, LDH, ALP), (in rare cases, clinical hepatitis has been reported, reversible upon discontinuation of diltiazem; see Section 4.4), thirst, vomiting, weight increase.

Dermatological

Petechiae, photosensitivity, pruritus, urticaria.

Other

Amblyopia, CPK increase, dyspnoea, epistaxis, eye irritation, hyperglycaemia, hyperuricaemia, impotence, muscle cramp, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

Post-marketing Experience

The following postmarketing 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 and toxic epidermal necrolysis), exfoliative dermatitis, acute generalised exanthematous pustular dermatitis, 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 is yet to be established. Bronchospasm (including asthma aggravation) has also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

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 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, 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 (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.

Symptoms and signs of overdose may be delayed due to the controlled release properties of the product, so patients should be kept under observation for at least 24 hours.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of Action

Diltiazem hydrochloride produces its antihypertensive effects 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 normotensives.

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 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. Increased heart failure has, however, been reported in occasional patients with pre-existing impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the 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 with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem reverses the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem 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 conventional diltiazem hydrochloride 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 hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval but has not usually produced abnormal prolongation (see Section 4.4).

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* ligand binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem 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. Minimum therapeutic plasma levels of diltiazem appear to be in the range of 50 - 200 ng/mL.

There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

No studies have been conducted in patients with gastrointestinal disease. As with other modified release oral preparations, patients with diarrhoea or colonic disease may have impaired absorption due to a shortened gastric transit time.

DILTIAZEM SANDOZ CD Capsules

When compared to a diltiazem tablet at steady-state, more than 95% of drug is absorbed from the Diltiazem Sandoz CD capsule formulation. A single 360 mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours.

When Diltiazem Sandoz CD was coadministered with a high fat content breakfast, the absorption of diltiazem was delayed but the extent of diltiazem absorption and total bioavailability were not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with diltiazem tablets and diltiazem SR capsules is observed. As the dose of Diltiazem Sandoz CD capsules is increased from a daily dose of 120 mg to 240 mg, there is

an increase in the area-under-the curve of 2.7 times. When the dose is increased from 240 mg to 360 mg there is an increase in the area-under-the curve of 1.6 times.

A single capsule of Diltiazem Sandoz CD 360 mg was found to be bioequivalent to two Diltiazem Sandoz CD 180 mg capsules.

No information is available regarding the pharmacokinetics and bioavailability of diltiazem in the CD or SR capsule form in patients with hepatic or renal failure, or in elderly hypertensive patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 180 and 240 mg capsules contain the following inactive ingredients: fumaric acid, purified talc, colloidal anhydrous silica, nonpareil seeds (PI 1366), white beeswax, ethylcellulose, castor oil, stearic acid, tributyl acetylcitrate, simethicone and methacrylic acid copolymers (Eudragit RS 30D and Eudragit RL 30D) and gelatin. In addition the following dyes are used: brilliant blue FCF, titanium dioxide and black iron oxide.

The 360 mg capsules contain the following inactive ingredients: nonpareil seeds (PI 1366), povidone, sodium lauryl sulfate, diethyl phthalate, purified talc, methacrylic acid copolymers (Eudragit RS 30D and Eudragit RL 30D), tributyl acetylcitrate, simethicone, titanium dioxide, brilliant blue FCF and gelatin.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light and moisture. Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Diltiazem Sandoz CD capsules are packaged in high density polyethylene bottles with child resistant closures in packs of 7 and 30, and 360 mg capsules are also available in packs of 10 and 28.

Not all pack sizes may be marketed.

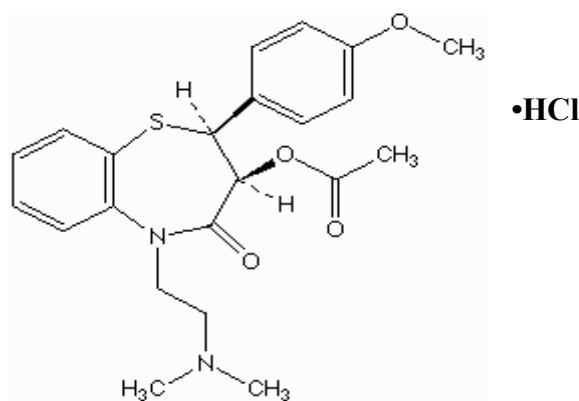
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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



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. It has a molecular weight of 450.98.

CAS Number

CAS 33286-22-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

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12-24 Talavera Road
Macquarie Park NSW 2113
Australia

Supplier

Sandoz Pty Ltd
54 Waterloo Road,
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Australia

9 DATE OF FIRST APPROVAL

26 February 2007

10 DATE OF REVISION

17 April 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Movement of text and updates to headings to align with the revised PI format
4.4, 4.5, 4.8	Revision or addition of safety information in regards to co-administration with beta-blockers and depression
4.4, 4.5, 4.6, 4.8, 4.9, and 6.1	Minor editorial changes