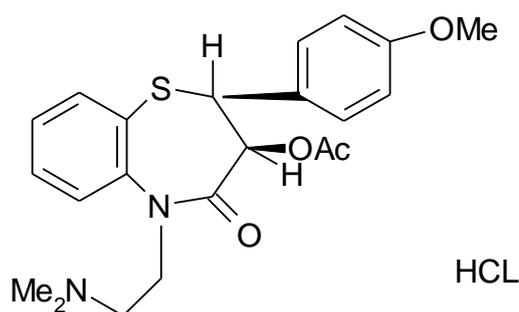


PRODUCT INFORMATION
DILTIAZEM SANDOZ® 60MG FILM-COATED TABLETS

NAME OF THE MEDICINE

Chemical name: (2*S*,3*S*)-5-(2-dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate hydrochloride.

Generic name: diltiazem hydrochloride.



CAS 33286-22-5

MW: 450.98

DESCRIPTION

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

Composition

Each tablet contains:

Active ingredient:

Diltiazem Hydrochloride 60.00mg

Inactive excipients:

Hydrogenated Castor Oil, Lactose, Povidone 25, Macrogol 6000, Microcrystalline Cellulose, Sodium Starch Glycollate, Colloidal Anhydrous Silica, Magnesium Stearate, Hypromellose, Stearic Acid, Titanium Dioxide.

PHARMACOLOGY

Diltiazem is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist).

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.

Mechanism of Action. Although the 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 increase in coronary blood flow (epicardial and subendocardial) occur in ischaemic and nonischaemic models and are accompanied by dose dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Haemodynamic and electrophysiological 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 atrial-His (A-H) interval can be seen at higher doses.

In humans, 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 end diastolic pressure have not been affected. There are as yet few data on the interaction of Diltiazem and β -blockers. Resting heart rate is usually unchanged or slightly reduced by Diltiazem.

Intravenous Diltiazem hydrochloride in doses of 20mg prolongs atrial-His conduction time and atrioventricular node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of Diltiazem 300mg in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first degree atrioventricular block. Diltiazem associated prolongation of the atrial-His 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 240mg/day has resulted in small increases in PK interval but has not usually produced abnormal prolongation. There were, however, three instances of second degree atrioventricular block and one instance of third degree atrioventricular block in a group of 959 chronically treated patients.

Pharmacokinetics

Diltiazem 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 Diltiazem 30 to 120mg 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 to 7 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 nanogram/mL. There is a departure from dose linearity when single doses above 60mg are given; a 120mg dose gave blood levels three times that of the 60mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of Diltiazem.

INDICATIONS

Moderate to severe angina pectoris due to atherosclerotic coronary artery disease or coronary artery spasm (vasospastic angina).

CONTRAINDICATIONS

- Sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- Hypotension (less than 90mmHg systolic).
- Severe congestive heart failure.
- Severe bradycardia (below 40bpm).
- Concomitant use of dantrolene infusion (see INTERACTIONS WITH OTHER MEDICINES).
- Idiosyncrasy or hypersensitivity to Diltiazem or any of the excipients listed under Description.
- Breastfeeding.
- Left ventricular failure with pulmonary congestion
- Patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.
- Second or third degree AV block except in the presence of a functioning ventricular pacemaker
- Combination with ivabradine.

PRECAUTIONS

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 atrioventricular 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 atrioventricular block (6 of 1,243 patients or 0.48%). Concomitant use of Diltiazem with β -blockers or digitalis may result in additive effects on cardiac conduction (see also INTERACTIONS WITH OTHER MEDICINES). A patient with Prinzmetal angina developed periods of asystole (2 to 5 seconds) after a single dose of Diltiazem 60mg.

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 β -blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients (see also INTERACTIONS WITH OTHER MEDICINES).

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

Acute hepatic injury. In rare instances, significant elevations in enzymes such as alkaline phosphatase, 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 Adverse Effects).

Concomitant administration with beta-blockers. Controlled and uncontrolled studies suggest that concomitant use of Diltiazem and β -blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. (see also INTERACTIONS WITH OTHER MEDICINES).

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 by approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted.

Abrupt withdrawal. The sudden withdrawal of Diltiazem has been associated with severe angina.

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.

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. Tablet residues from slow release formulations of the product may pass into the patient's stools.

Use with caution in the following circumstances

Impaired hepatic or renal function.

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 the bile. As with any drug given over long periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. 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 125mg/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 20mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events. Dermatological events (see ADVERSE EFFECTS) 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 diabetic patients. 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 two to six months of Diltiazem administration. Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

Use with amiodarone. Amiodarone should be used with caution with Diltiazem particularly if there is suspicion of underlying dysfunction of sinus node, such as bradycardia or sick sinus syndrome or if there is partial atrioventricular block (see also Interactions with other medicines).

Concomitant use with digoxin. Diltiazem has been shown to increase serum Digoxin concentrations and to modify its pharmacokinetics (see, Interactions with other medicines). Patients with plasma Digoxin levels in the upper therapeutic range (1.5 to 2.5 nanogram/mL) may develop toxic plasma concentrations and side effects. Therefore, digoxin plasma concentrations should be controlled six to eight 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 one year) with doses higher than 240mg/day are limited. Therefore long-term treatment with doses exceeding 240mg/day is not recommended.

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 perinatal/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. Accordingly, Diltiazem is not recommended during pregnancy, as well as in women of child-bearing potential not using effective contraception.

Australian categorisation definition of Category C. Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Use in lactation.

Diltiazem levels were measured in both serum and milk in breastfeeding women. Samples were taken simultaneously on the fourth day of the treatment with Diltiazem 60mg four times a day. The peak level in milk was as high as 200 nanogram/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 infant.

Therefore, breastfeeding while taking Diltiazem is contraindicated. If use of Diltiazem is medically essential, an alternative method of infant feeding should be instituted.

Paediatric use

Safety and effectiveness in children have not been established.

Use in the elderly. Administration of Diltiazem to elderly patients (≥ 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 also DOSAGE AND ADMINISTRATION).

INTERACTIONS WITH OTHER MEDICINES

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 coadministered 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 P450 mixed function oxidase. Co-

administration of Diltiazem with other agents that 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.

Ivabradine

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

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

Downward titration of cyclosporin dose may be required to minimise the risk of nephrotoxic potential.

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.

Beta-blockers. Controlled and uncontrolled studies suggest that concomitant use of Diltiazem and β -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 of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an increase 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.

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. Increase 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 co-administration. 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 increase plasma Diltiazem concentrations. Patients receiving Diltiazem concurrently with 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 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.

Rimonabant. Co-administration with diltiazem results in an increase in serum rimonabant levels.

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 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 PRECAUTIONS,). 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.

Nitrate Derivatives. 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 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 20mg dose of simvastatin in 10 healthy volunteers, after 2 weeks of 120mg of diltiazem sustained release capsules 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 dosage range.

In another 10 volunteer study, the co-administration of 120mg of diltiazem sustained release capsules 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 sustained release capsules 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.

Grape fruit juice. Grape fruit juice may increase diltiazem exposure. Patients who consume grape fruit juice should be monitored for increased effects of diltiazem. Grape fruit 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 received diltiazem and X-ray contrast media.

Benzodiazepines (midazolam, triazolam): Diltiazem significantly increases plasma concentrations of midazolam and triazolam and prolongs their half-life. Special care should be taken when prescribing short-acting benzodiazepines metabolized 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.

ADVERSE EFFECTS

More Common reactions

In clinical trials of Diltiazem in anginal patients, the most common events (i.e. greater than 1%) were oedema (2.4%), headache (2.1%), nausea (1.9%), atrioventricular block (1.6%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), urticaria, palpitations, constipation, dyspepsia, gastric pain, malaise, erythema, flushing, lower limb oedema and light headedness.

Less common reactions

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular. Angina, arrhythmia, first degree atrioventricular block, second or third degree atrioventricular block (see PRECAUTIONS), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

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

Gastrointestinal. Anorexia, constipation, diarrhoea, dry mouth, dysgeusia, dyspepsia, gastric pain, mild elevations of alkaline phosphatase, hepatic enzymes increase (AST, ALT, ALP and LDH) (in rare cases, clinical hepatitis has been reported, reversible upon discontinuation of Diltiazem, see PRECAUTIONS.), thirst, vomiting, weight increase.

Dermatological. Petechiae, erythema, photosensitivity, pruritus, urticaria

Other Amblyopia, creatine phosphokinase elevation, dyspnoea, epistaxis, eye irritation, hyperglycaemia, hyperuricaemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

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, 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 Stevens-Johnson syndrome), exfoliative dermatitis, acute generalised exanthematous pustular dermatitis, sino-atrial block, orthostatic hypotension, malaise, extrapyramidal symptoms, gingival hyperplasia, haemolytic anaemia, increased bleeding time, leucopenia, 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 leucocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and Diltiazem therapy is yet to be established.

DOSAGE AND ADMINISTRATION

Angina. Dosage must be adjusted to each patient's needs. Starting with 30mg 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 240mg daily. The maximum recommended dose is 360mg 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 (> 65 years old) suggest that a lower dosage might be required in this age group (see also PRECAUTIONS).

Use in patients with renal or hepatic impairment

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

Concomitant use with other antianginal and antihypertensive agents - Sublingual glyceryl trinitrate may be taken as required to abort acute anginal attacks during Diltiazem therapy .

Prophylactic nitrate 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 PRECAUTIONS,

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.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for the advice on management of overdose.

The oral LD₅₀ values in mice and rats range from 415 to 740mg/kg and from 560 to 810mg/kg respectively. The intravenous LD₅₀ values in these species were 60 and 38mg/kg respectively. The oral LD₅₀ value in dogs is considered to be in excess of 50mg/kg, while lethality was seen in monkeys at 360mg/kg. The toxic dose in humans 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 1g to 10.8g. 16 of these reports involved multiple drug ingestions. 22 reports indicated patients had recovered from Diltiazem overdose ranging from less than 1g to 10.8g. 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.

Symptoms. Events observed following Diltiazem overdose included bradycardia, hypotension, heart block and cardiac failure and atrio-ventricular conduction disturbances.

Treatment. 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 gastric lavage. Diltiazem does not appear to be removed by peritoneal dialyses 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 1.0mg). If there is no response to vagal blockade administer isoprenaline cautiously.

High degree atrioventricular block. Treat as for bradycardia above. Fixed high degree atrioventricular block should be treated with cardiac pacing.

Cardiac failure. Administer inotropic agents (isoprenaline, dopamine or dobutamine) and diuretics.

Hypotension. Administer vasopressors (dopamine or noradrenaline acid tartate).

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

PRESENTATION AND STORAGE CONDITIONS

Diltiazem Sandoz 60mg tablets are white, round, biconvex tablets with one sided score notch, packaged in blisters and bottles of 90 tablets.

Store below 25°C.

Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

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Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine.

Date of first inclusion on the Australian Register of Therapeutic Goods (the ARTG): 07 September 2009

Date of last amendment: 13/02/2017