TERRY WHITE CHEMISTS DILTIAZEM TABLETS

NAME OF THE MEDICINE
Diltiazem hydrochloride.

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

\[
\text{\[
\begin{array}{c}
\text{S} \\
\text{H} \\
\text{OAc} \\
\text{OMe} \\
\text{NMe}_2 \\
\text{H} \\
\text{1HCl}
\end{array}
\]
}\]

Molecular Formula: \(\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S.HCl}\)

CAS Number: 33286-22-5

Diltiazem hydrochloride has a molecular weight of 451.

DESCRIPTION
Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform.

PHARMACOLOGY
Pharmacodynamics
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. \textit{Angina due to Coronary Artery Spasm:}
   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. \textit{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 sub-maximal 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 subendocardial) occur in ischaemic and non-ischaemic 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 sino-atrial 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 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. In exercise tolerance studies in patients with ischaemic heart disease, diltiazem 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. 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 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.

Pharmacokinetics

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 90% 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.
INDICATIONS
Patients with 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.
- 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.
- Idiosyncrasy or hypersensitivity to diltiazem or any of the excipients listed under PRESENTATION AND STORAGE CONDITIONS.
- Patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.
- Severe bradycardia (below 40 bpm).
- Concomitant use of dantrolene infusion (see Interactions with Other Medicines).
- Breastfeeding.
- Left ventricular failure with pulmonary congestion.

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 ECG (risk of exacerbation and rarely of complete block) or prolonged PR interval,

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 (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta blockers or digoxin may result in additive effects on cardiac conduction (see also PRECAUTIONS, Concomitant Administration with Beta-Blockers). 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 also PRECAUTIONS, Concomitant Administration with Beta-Blockers).

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, SGOT, SGPT 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 PRECAUTIONS and ADVERSE EFFECTS).

Concomitant Administration with Beta-Blockers
Controlled and uncontrolled studies suggest that the concomitant use of diltiazem and beta blockers or digoxin 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 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 (see PRECAUTIONS, Cardiac Conduction and Congestive Heart Failure).

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

Impaired Hepatic or Renal Function
Plasma diltiazem concentrations can be increased in patients with renal or hepatic insufficiency. Diltiazem 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. 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 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.

Dermatological Events
Dermatological events (see ADVERSE EFFECTS) may be transient and may disappear despite continued use of diltiazem. However, skin eruption 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.

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 also Interaction with Other Medicines).

Concomitant Use of Digoxin
Diltiazem has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics (see Interaction with Other Medicines). Patients with plasma digoxin levels in the upper therapeutic range (1.5 to 2.3 nmol/L) may develop toxic plasma concentrations and adverse effects. Therefore, digoxin plasma concentrations should be monitored for 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.

Paediatric Use
Safety and effectiveness of diltiazem in children have not been established.

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 contraindications and precautions should be carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment. 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 DOSAGE AND ADMINISTRATION).

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 tested in this class carry the potential for foetal hypoxia associated with maternal hypotension. Accordingly, diltiazem should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

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 diltiazem is contraindicated. If use of diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

Interaction 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.

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the CYP450 3A4 enzyme system. Other medicines that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other medicines that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels. 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.

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

1 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 foetus or neonate without causing malformations. These effects may be reversible.
cyclosporin dose be reduced, renal function be monitored, circulating cyclosporine levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.
Beta-Blockers
Controlled and uncontrolled studies suggest that concomitant use of 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 concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. 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 (see also PRECAUTIONS, Cardiac Conduction, Congestive Heart Failure and Concomitant Administration with Beta-Blockers).

Buspirone
In nine healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5 fold and Cmax 4.1 fold compared to placebo. The T1/2 and Tmax of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during co-administration, and should be based on clinical assessment.

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 (see CONTRAINDICATIONS).

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/min 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)
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. Ranitidine produced smaller, non-significant increases.

Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Benzodiazepines
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%.

Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3-4 fold and the Cmax by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increased (1.5-2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g., prolonged sedation) of both midazolam and triazolam.
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.

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 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 PRECAUTIONS, Use with Amiodarone). 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
Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment.

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.

Statins
Oral administration of diltiazem can raise the plasma concentration of drugs exclusively metabolised by CYP3A4.

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 Cmax versus lovastatin alone.

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

Other Antiarrhythmic Agents
Since diltiazem has antiarrhythmic properties, its concomitant use with other antiarrhythmic agents is not recommended. Such combination should only be used under close clinical and ECG monitoring.
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.

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%), AV block (1.6%), dizziness (1.5%), rash (1.3%),
asthenia (1.2%), urticaria and light-headedness.

Less Common Reactions
In addition, the following events were reported infrequently (less than 1%):

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

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

Gastrointestinal
Anorexia, constipation, diarrhoea, dry mouth, dysgeusia, dyspepsia, mild elevations of alkaline
phosphatase, SGOT, SGPT, and LDH (see PRECAUTIONS, Acute Hepatic Injury), thirst, vomiting,
weight increase.

Dermatological
Petechiae, photosensitivity, pruritus, urticaria.

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

The following post-marketing events have been reported infrequently in patients receiving diltiazem:
Alopecia, allergic reactions, 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, sino-atrial block, orthostatic hypotension, asystole, myopathy,
malaise, gastric pain, 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 of 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.
DOSAGE AND ADMINISTRATION

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.

Dosage 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 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 anti-anginal effectiveness of this combination.

Beta-Blockers  see PRECAUTIONS.

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

OVERDOSAGE

Symptoms
Due to the nature of the drug, one might expect lengthening of the PR interval, sino-atrial node dysfunction, hypotension and cardiac failure.

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 reports of diltiazem overdose in doses ranging from less than 1 g to 18 g. Of cases with known outcome, most patients recovered and in cases with a fatal outcome, the majority involved multiple drug ingestion.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favourably to atropine as did heart block, although cardiac pacing was also frequently utilised to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.
Treatment
In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. 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 judgment and experience of the treating physician.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS
Packs of 90 tablets.

Terry White Chemists Diltiazem Tablets 60 mg are round, white, biconvex, film-coated tablets, scored and engraved “APO” over “D60” on one side and the other side plain.

AUST R 73851.

Each Terry White Chemists Diltiazem tablet contains 60 mg diltiazem hydrochloride for oral administration.

Each GenRx Chemmart Terry White Chemists Diltiazem tablet also contains as inactive excipients the following: lactose, hypromellose, magnesium stearate, anhydrous colloidal silica, macrogol 3350, and titanium dioxide.

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

NAME AND ADDRESS OF THE SPONSOR
Apotex Pty Ltd
ABN 52 096 916 148
66 Waterloo Road
North Ryde NSW 2113
Australia
DISTRIBUTOR
Symbion Pharmacy Services Pty Ltd
ABN 25 000 875 034
48-58 Overseas Drive
Noble Park North VIC 3174
Australia

Terry White Chemists is a registered trade mark of Symbion Pharmacy Services Pty Ltd

POISONS SCHEDULE
S4: Prescription Only Medicine

Date of TGA approval : 16 May 2000
Date of most recent amendment : 11 July 2008