NAME OF THE MEDICINE
Diltiazem hydrochloride.

Chemical Name: Hydrochloride salt of (2S, 3S)-5-(2-dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazapin-3-yl acetate.

The Structural Formula is shown below:

Molecular Weight: 450.98
CAS Number: 33286-22-5

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

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

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 normotensive individuals.

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 left ventricular and 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 β-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 hydrochloride in doses of 20 mg prolongs A-H conduction time and atrioventricular 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 P-R prolongation was 14% with no instances of greater than first degree atrioventricular block. Diltiazem associated prolongation of the A-H 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 P-R interval but has not usually produced abnormal prolongation (see PRECAUTIONS).

**Pharmacokinetics**

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 to 4½ 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 therapeautic plasma levels of diltiazem appear to be in the range 50 to 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 CD Capsule Pharmacokinetics**

After a single 240 mg dose of Diltiazem CD to healthy volunteers, the maximum plasma level of diltiazem averaged 113 ng/mL, the elimination half life 6.1 hours and the AUC 2237 ng.h/mL. After a high fat breakfast, the maximum plasma level of diltiazem averaged 93 ng/mL, the elimination half life 6.3 hours and the AUC 1992 ng.h/mL. Dose dumping did not occur.

No information is available regarding the pharmacokinetics and bioavailability of Diltiazem CD capsules in patients with hepatic or renal failure, or elderly hypertensive patients.
INDICATIONS

Treatment of mild to moderate essential hypertension.

Management of chronic stable angina (effort associated angina) where there is no evidence of vasospastic or unstable angina. Because the safety and efficacy of CD capsules in the management of unstable or vasospastic angina have not been substantiated, use of this formulation for these indications is not recommended.

CONTRAINDICATIONS

Sick sinus syndrome except in the presence of a functioning ventricular pacemaker.

Second or third degree atrioventricular block except in the presence of a functioning ventricular pacemaker.

Hypotension (less than 90 mmHg systolic).

Congestive heart failure.

Idiosyncrasy or hypersensitivity to diltiazem or any of the excipients listed under PRESENTATION AND STORAGE CONDITIONS.

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 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 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 (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with β-blockers or digitalis may result in additive effects on cardiac conduction (see also PRECAUTIONS, Concomitant Administration with Beta-Blockers). A patient with Prinzmetal angina developed periods of asystole (2 to 5 seconds) after a single dose of diltiazem hydrochloride 60 mg.

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 ± 6%) showed improvement in indices of ventricular function without significant decreases in contractile function (dp/dt). Experience with the use of diltiazem in combination with β-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination (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
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 (e.g. alkaline phosphatase, LDH, AST, and 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 ADVERSE EFFECTS).

Concomitant Administration with Beta-Blockers
Controlled and uncontrolled studies suggest that concomitant use of diltiazem and β-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 (see also PRECAUTIONS, Cardiac Conduction and Congestive Heart Failure).

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.

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

Impaired Hepatic and 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 new 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 CD. 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 two to six 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 atrioventricular block (see PRECAUTIONS, Interactions with Other Drugs).
Concomitant Use with Digoxin
Diltiazem has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics (see PRECAUTIONS, Interactions with Other Drugs). 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 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 or treatment 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.

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 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\(^1\))
Reproduction studies have been conducted in mice, rats and rabbits. Administration of high doses has resulted in embryonic and fetal 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 to produce fetal hypoxia associated with maternal hypotension. Accordingly, diltiazem should not be used in pregnant women unless the potential benefit outweighs the risk to the fetus.

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 hydrochloride 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 infant.

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

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

No pharmacokinetic interaction studies have been conducted with Diltiazem CD. However, interactions reported with a conventional diltiazem formulation are still relevant. As with all drugs, care should be

\(^1\) 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. Accompanying text above should be consulted for further details.
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 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 CD 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.

**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. Downward titration of cyclosporin dose may be required to minimise the risk of nephrotoxic potential. It is recommended that the 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 domestic studies suggest that concomitant use of diltiazem and β-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 the bioavailability of propranolol was increased by 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/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)**
Concurrent administration of cimetidine produced an increase in single dose diltiazem levels
(approximately 50% over control). The plasma levels of diltiazem's metabolite, desacetyldiltiazem, were also increased. 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 slow release diltiazem twice daily, resulted in significantly (p<0.05) increased mean peak serum concentrations 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 for simvastatin and simvastatin acid. Concomitant use of Diltiazem CD with simvastatin should be undertaken with caution, particularly at the higher end of the dosing range.

In another 10 volunteer study, the coadministration of 120 mg slow-release diltiazem 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.

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

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 usually been excluded from these studies.

Table 1 presents the most common adverse reactions reported in placebo controlled angina and hypertension trials in patients receiving an extended release diltiazem formulation, up to 360 mg, with rates in placebo patients shown for comparison.

Table 1

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>DILTIAZEM (n=607)</th>
<th>PLACEBO (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Atrioventricular block (first degree)</td>
<td>3.3%</td>
<td>-</td>
</tr>
<tr>
<td>Oedema</td>
<td>2.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>ECG abnormality</td>
<td>1.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.8%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
In clinical trials of diltiazem as CD capsules, tablets and SR capsules involving 3,200 patients, the most common events (i.e. > 1%) were oedema (4.6%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first degree atrioventricular block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%) and dyspepsia (1.2%).

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

**Cardiovascular**
Angina, arrhythmia, atrioventricular block (second or third degree), 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, mild elevations of AST, ALT, LDH, and alkaline phosphatase (in rare cases, clinical hepatitis has been reported, reversible upon discontinuation of diltiazem CD; see **PRECAUTIONS**, Acute Hepatic Injury), thirst, vomiting, weight increase.

**Dermatological**
Petechiae, photosensitivity, pruritis, urticaria.

**Other**
Amblyopia, creatine kinase (CK) increase, dyspnoea, epistaxis, eye irritation, hyperglycaemia, hyperuricaemia, impotence, muscle cramp, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties. The following postmarketing events have been reported infrequently in patients receiving diltiazem; alopecia, allergic reactions, gynaecomastia, vasculitis, musculo-cutaneous reactions such as simple erthema 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 exanathematous 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. 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. 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**
Capsules should be swallowed whole without chewing.

Patients controlled on diltiazem alone or in combination with other medications may be safely switched to Diltiazem 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 blood pressure should be done initially to ensure blood pressure control lasts over dosing interval. 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. Monitoring of trough blood pressure should be done initially to ensure control lasts over dosing period.

**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 have not been fully elucidated. Preliminary results in elderly patients (> 65 years of age) suggest that a lower dosage might be required in this age group (see PRECAUTIONS).

**Impaired Hepatic or Renal Function**

There are few available data concerning dosage requirements in patients with impaired renal or hepatic function. If diltiazem must be used in these patients, the dosage should be carefully and gradually adjusted depending on patient tolerability and responses (see PRECAUTIONS).

**Concomitant Use with Other Cardiovascular Agents**

Sublingual Glyceryl Trinitrate

Sublingual glyceryl trinitrate (GTN) may be taken as required to abort acute anginal attacks during Diltiazem CD therapy.

Prophylactic Nitrate Therapy

Diltiazem CD may be safely co-administered with short and long acting nitrates.

**Beta-Blockers**: see PRECAUTIONS.

**Antihypertensives**

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

**OVERDOSAGE**

The oral LD<sub>50</sub> values in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD<sub>50</sub> values in these species were 60 and 38 mg/kg respectively. The oral LD<sub>50</sub> 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 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 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 gastrointestinal decontamination. Symptoms and signs of overdose may be delayed due to the controlled release properties of these products, so patients should be kept under
observation for at least 24 hours. Diltiazem does not appear to be removed by peritoneal dialysis or haemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered.

**Bradycardia**
Administer atropine (0.6 to 1.0 mg). 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**
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 doctor.

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

**PRESENTATION AND STORAGE CONDITIONS**
GenRx Diltiazem CD 180 mg capsules have a light turquoise body and light blue cap. They are imprinted “APO 180” in white ink. Available in blister or bottle packs of 30. AUST R 80555 and AUST R 90918.

GenRx Diltiazem CD 240 mg capsules have a light blue body and cap. They are imprinted “APO 240” in white ink. Available in blister or bottle packs of 30. AUST R 80553 and AUST R 90922.

Each GenRx Diltiazem CD capsule contains diltiazem hydrochloride in a blend of beads with controlled dissolution characteristics for once a day administration.

Each capsule also contains the following inactive ingredients: methylcellulose, microcrystalline cellulose, tributyl citrate, polysorbate 80, talc, Eudragit RS 30D, methacrylic acid copolymer, gelatin; Brilliant blue FCF CI 42090, titanium dioxide as dyes and TekPrint SB-0007P White Ink for imprinting.

Store below 25°C. Protect from moisture.

**NAME AND ADDRESS OF THE SPONSOR**
Apotex Pty Ltd
ABN 52 096 916 148
66 Waterloo Road
North Ryde NSW 2113
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GenRx is a registered trademark of Apotex Pty Ltd.

**POISON SCHEDULE OF THE MEDICINE**
S4: Prescription Only Medicine

Date of TGA approval : 30 April 2002

Date of most recent amendment : 11 July 2008