

# DATA SHEET

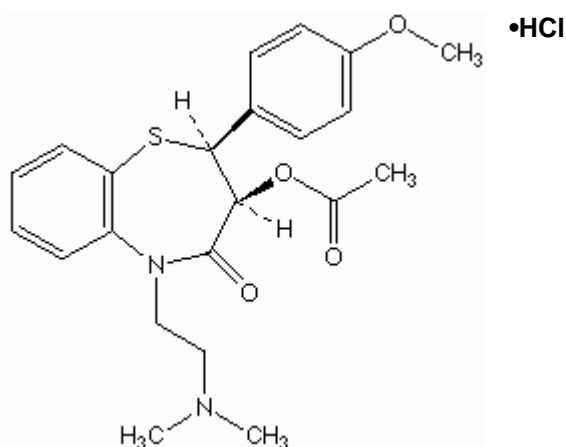
## CARDIZEM<sup>®</sup> TABLETS

### NAME OF THE MEDICINE

Diltiazem hydrochloride

### DESCRIPTION

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



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

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is freely soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains 60mg diltiazem hydrochloride for oral administration. Cardizem tablets also contain lactose, microcrystalline cellulose, hypromellose, silica-colloidal anhydrous, magnesium stearate, methylhydroxy benzoate, colouring (Quinoline Yellow CI 47005 & Sunset Yellow FCF CI 15985) and a film coating (Opadry YS-5-7044 and methylhydroxy benzoate).

### PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM 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, CARDIZEM is believed to act in the following ways:

#### 1. Vasospastic angina

CARDIZEM 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 CARDIZEM.

## 2. Exertional angina

CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand and increase oxygen supply. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads and by dilating coronary arteries.

In animal models, diltiazem interferes with the slow inward (depolarising) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and sub-endocardial) occur in ischaemic and nonischaemic models and are accompanied by dose dependent decreases in systemic blood pressure and decreases in peripheral resistance.

### Haemodynamic and Electrophysiologic Effects

Like some other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergometrine provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischaemic heart disease, reduces the heart rate/blood pressure product for any given workload. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction and left ventricular end-diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM 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 CARDIZEM 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 and Metabolism

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%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM 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 CARDIZEM 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 CARDIZEM 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 CARDIZEM.

## **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
- Severe bradycardia (below 40 bpm)
- 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.

## **PRECAUTIONS**

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.

### **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).

CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second or third degree AV block (six of 1,243 patients or 0.48%). Concomitant use of CARDIZEM with beta-blockers or digitalis may result in additive effects on cardiac conduction (see also Interactions with Other Medicines). A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg CARDIZEM.

### **Congestive Heart Failure**

Although CARDIZEM 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 CARDIZEM 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 Interactions with Other Medicines).

## **Hypotension**

Decreases in blood pressure associated with CARDIZEM 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 CARDIZEM is uncertain in most cases, but probable in some (see ADVERSE EFFECTS).

## **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 closed monitoring, particularly of heart rate, should be carried out at the beginning of treatment.

CARDIZEM (diltiazem hydrochloride) is extensively metabolised by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. Cardizem should be used with caution in patients with renal or hepatic impairment. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of CARDIZEM 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 CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported. Should dermatological reactions persist, the drug should be discontinued.

## **Use in Diabetics**

CARDIZEM should be used with caution in patients suffering from diabetes. Like other calcium channel blockers, CARDIZEM 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 CARDIZEM administration.

## **Concomitant Administration with Beta-blockers**

Controlled and uncontrolled studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities (see also Interactions with Other Medicines).

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

## **Use with Amiodarone**

Amiodarone should be used with caution with CARDIZEM 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 Interactions with Other Medicines).

### **Concomitant Use of Digoxin**

CARDIZEM has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics (see also Interactions with Other Medicines). Patients with plasma digoxin levels in the upper therapeutic range (1.5 to 2.5 ng/mL) may develop toxic plasma concentrations and side effects. Therefore, digoxin plasma concentrations should be controlled 6 to 8 days after starting these drug combinations, at which time new steady state conditions develop and the digoxin dose can be reduced if there is evidence of toxicity.

### **Long Term Use**

Data to support long-term use of CARDIZEM (longer than 1 year) with doses higher than 240 mg/day is limited. Therefore the long-term treatment with doses exceeding 240 mg/day is not recommended.

### **Abrupt withdrawal**

The sudden withdrawal of CARDIZEM has been associated with severe angina.

### **Paediatric Use**

Safety and effectiveness in children have not been established. Therefore, diltiazem is not recommended for use in children.

### **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, CARDIZEM is a calcium channel blocker and drugs listed in this class carry the potential for foetal hypoxia associated with maternal hypotension. CARDIZEM is therefore not recommended during pregnancy, as well as in women of child-bearing potential not using effective contraception.

### **Use in Lactation**

CARDIZEM levels were measured in both serum and milk in nursing women. Samples were taken simultaneously on the fourth day of the treatment with CARDIZEM 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 CARDIZEM is freely diffusible in milk but it is not known whether it is harmful to the newborn. Therefore, breastfeeding while taking this drug should be avoided. If use of Cardizem is considered medically essential, an alternative method of infant feeding should be instituted.

### **Use in Elderly**

Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. Plasma diltiazem concentrations can be increased in the elderly. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include: peripheral oedema, bradycardia, palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable. (See DOSAGE AND ADMINISTRATION)

### **Interactions with Other Medicines**

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

Diltiazem is metabolised by CYP3A4. A moderate (less than 2-fold) increase of diltiazem plasma concentration in cases of co-administration with a stronger CYP3A4 inhibitor has been documented. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plasma concentration of either co-administered drug. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition or induction of metabolism. This may lead to an increased risk of adverse reactions.

#### Dantrolene infusion

Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of a calcium channel antagonist and dantrolene is therefore potentially dangerous.

#### 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.

#### Rifampicin

There is a risk of decreased diltiazem plasma levels after initiating therapy with rifampicin. The patient should be carefully monitored when initiating or discontinuing rifampicin treatment.

#### Corticosteroids (methylprednisolone)

Concomitant administration has resulted in the inhibition of methylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein. The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.

#### Benzodiazepines (midazolam, triazolam)

Diltiazem significantly increases plasma concentration of midazolam and triazolam and prolongs their half-life. Special care should be taken when prescribing short-acting benzodiazepines metabolised by the CYP3A4 pathway in patients using diltiazem.

#### Beta-blockers

Controlled and uncontrolled studies suggest that concomitant CARDIZEM 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 CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted.

Due to the possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sinoatrial 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 CARDIZEM and digoxin may result in additive effect on conduction. CARDIZEM 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  $86.9 \pm 18.3$  to  $62.8 \pm 15.4$  mL/minute and digoxin elimination half-life was prolonged from  $36.7 \pm 11.2$  to  $44.5 \pm 11.5$  hours during CARDIZEM coadministration. There is an increased risk of bradycardia with this combination. Caution is required when digoxin is combined with diltiazem, particularly in elderly and when high doses are used.

### H<sub>2</sub> antagonists (cimetidine, ranitidine)

Concomitant use may result in increased plasma diltiazem concentrations. Patients receiving diltiazem concurrently with an H<sub>2</sub> antagonist should be carefully monitored when initiating or discontinuing therapy with H<sub>2</sub> antagonists. An adjustment in diltiazem daily dose may be necessary.

Concurrent administration of cimetidine produced an increase in single dose CARDIZEM levels (approximately 50% over control). The plasma levels of CARDIZEM's metabolite, desacetyldiltiazem were also increased.

### Diazepam

Diazepam has been reported to cause a significant decrease in CARDIZEM plasma levels. The average decrease in CARDIZEM 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.

### 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 life-threatening low cardiac output state developed when amiodarone was added to a regimen of CARDIZEM and a diuretic. It has been suggested that CARDIZEM 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.

### Short and long acting nitrates

Increased hypotensive effects and faintness may be seen due to additive vasodilating effects. In patients treated with calcium channel antagonists, the addition of nitrate derivatives should only be carried out at gradually increasing doses.

### Anaesthetic agents

Additive haemodynamic depressive effects are found when calcium channel blockers are combined with inhalation anaesthetic agents such as halothane, isoflurane or enflurane. These effects are related both to the anaesthetic concentration and to the dose of the calcium channel blocker. Depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment.

### Statins

Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis due to statins metabolised by CYP3A4 may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.

Administration of a single 20 mg dose of simvastatin in 10 healthy volunteers, after 2 weeks of 120 mg of CARDIZEM SR twice daily, resulted in a significantly ( $p < 0.05$ ) increased mean peak serum concentration of simvastatin by 3.6 fold and simvastatin acid by 3.7 fold, the AUC by 4.8 fold for simvastatin and the elimination half-life by 2.3 fold. There was no change in the time to peak concentration curve for simvastatin and simvastatin acid. Concomitant use of CARDIZEM with simvastatin should be used with caution, particularly at the higher end of the dosing range.

In another 10 volunteer study, the coadministration of 120 mg of CARDIZEM SR twice daily with lovastatin resulted in a 3-4 times increase in mean lovastatin AUC and C<sub>max</sub> versus lovastatin alone.

No change in pravastatin AUC and C<sub>max</sub> was observed during CARDIZEM 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 (additive risk of increased cardiac adverse effects). Such combination should only be used under close clinical and ECG monitoring.

## **ADVERSE EFFECTS**

### **More Common Reactions**

In clinical trials of diltiazem in anginal patients, the most common events (ie. 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, palpitations, constipation, dyspepsia, gastric pain, malaise, erythema, flushing, lower limb oedema and lightheadedness.

### **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), 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, somnolence, tinnitus, tremor.

## **Gastrointestinal**

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

## **Dermatological**

Petechiae, photosensitivity, pruritus, urticaria.

## **Other**

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

The following post-marketing events have been reported infrequently in patients receiving diltiazem: mood changes (including depression), 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 Steven-Johnson's syndrome), exfoliative dermatitis, acute generalised exanthematous pustular dermatitis, sino-atrial block, orthostatic hypotension, malaise, gastric pain, extrapyramidal symptoms, gingival hyperplasia, haemolytic anaemia, increased bleeding time leukopenia, purpura, retinopathy and thrombocytopenia. Very rare cases of toxic epidermal necrolysis have also been reported. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of rash, characterised as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy cannot yet be established.

## **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.

### **Use in the elderly**

Pharmacokinetics of diltiazem in elderly patients has not been fully elucidated. Preliminary results in elderly patients (over 65 years old) suggest that a lower dosage might be required in this age group (see PRECAUTIONS).

### **Use in patients with renal or hepatic impairment**

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

### **OVERDOSAGE**

The oral LD<sub>50</sub> in mice and rats ranged from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD<sub>50</sub> in these species was 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 man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases. There have been 29 cases of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions. Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports involved with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, sinus bradycardia with or without isorhythmic dissociation, heart block, cardiac failure and atrio-ventricular conduction disturbances. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favourably to atropine as did heart block, although cardiac pacing was also frequently utilised to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or haemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

#### **Bradycardia**

Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoprenaline cautiously.

**High Degree AV Block**

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

**Cardiac Failure**

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

**Hypotension**

Vasopressors (eg, dopamine or noradrenaline acid tartrate).

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

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

**PRESENTATION AND STORAGE CONDITIONS**

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

CARDIZEM tablets are supplied in bottles of 7, 90 or 100\* tablets.

Protect from light and moisture. Store below 30°C.

\*Denotes presentations not available in New Zealand

**NAME AND ADDRESS OF THE SPONSOR**

sanofi-aventis new zealand ltd  
Level 8, James and Wells Tower  
56 Cawley Street  
Ellerslie  
Auckland  
New Zealand

**MEDICINE CLASSIFICATION**

Prescription Only Medicine

**DATE OF PREPARATION**

23 March 2009