

# DATA SHEET

## DILZEM

**Diltiazem hydrochloride 30 mg & 60 mg tablets.**

### Presentation

DILZEM 30 mg Tablet: Diltiazem HCl 30 mg is a white, circular, film-coated, biconvex tablet of approximately 6mm diameter embossed "D" one side.

DILZEM 60 mg Tablet: Diltiazem HCl 60 mg is a white capsule shaped, film-coated tablet, 10mm in length and 5mm wide; with a breakline and 'DL60' engraved on one face.

### Uses

#### *Actions*

Diltiazem, a benzothiazepine, is a calcium antagonist, inhibiting calcium ion entry into smooth muscle cells by blockade of slow calcium channels. It is believed to act as follows:

Angina due to coronary artery spasm: Diltiazem is a potent dilator of both epicardial and subendocardial coronary arteries and it inhibits spontaneous coronary artery spasm.

Exertional angina: Diltiazem is able to produce increases in exercise tolerance via reduction in heart rate, systemic blood pressure and dilation of coronary arteries. In animal models diltiazem interferes with the slow inward (depolarising) current in excitable tissue producing: relaxation of coronary vascular smooth muscle, dilation of both large and small coronary arteries without inducing a negative inotropic effect, and increased coronary blood flow accompanied by dose dependent decreases in systemic blood pressure and peripheral resistance.

Evaluation of glucose and lipid homeostasis in diabetic and non-diabetic subjects treated with calcium antagonists indicates that diltiazem does not affect energy metabolism in the majority of individuals.

#### *Pharmacokinetics*

Diltiazem is almost completely absorbed after oral administration but first pass metabolism limits its systemic availability to about 50%. Although detectable in plasma between 30-60 minutes after administration, peak levels are normally achieved 2-4 hours after administration of the 30 mg or 60 mg tablets.

Diltiazem is distributed to the liver, kidney, lung, spleen, heart and brain with tissue concentration decreasing in that order. Plasma protein binding accounts for 77-86% of plasma diltiazem, 35-40% being bound to albumin and the rest to a-glycoprotein.

Diltiazem is extensively metabolised in the liver by deacetylation, N-demethylation and O-demethylation such that only 0.1-4% of unchanged diltiazem appears in the urine. Five metabolites have been

identified. Desacetyldiltiazem is normally present in plasma at levels of 10-20% of the parent medicine and is 25-50% as potent a vasodilator as diltiazem. Some studies have, however, shown that this metabolite can accumulate during multiple oral dosing and the plasma concentration may exceed that of the parent medicine. Another metabolite, N-mono-demethyl-diltiazem may be about 20% as potent as the parent medicine. The other metabolites are devoid of pharmacological activity.

Studies in rats have shown that after administration of <sup>14</sup>C-diltiazem, greater than 90% of the <sup>14</sup>C can be removed from urine and faeces in 72 hours. Excretion of diltiazem metabolites in the faeces seems to be the main route of elimination since more than 60% of the dose is excreted into the bile in 24 hours and 65% into the faeces in 72 hours. There is extensive enterohepatic circulation.

The plasma half-life of diltiazem is approximately 3.5 hours. Therapeutic blood levels appear to be in the range of 50-200 ng/mL.

Plasma levels above 50 ng/mL are achieved between 1-1.5 hours and are maintained for approximately 8 hours after administration of the 30 mg and 60 mg tablets.

Little information is available as to the effect of age, renal or hepatic dysfunction on the pharmacokinetic profile, other than that the more pronounced anti-hypertensive effect seen in the elderly may be due to a decreased clearance.

Diltiazem hydrochloride is excreted in breast milk.

### ***Indications***

Angina pectoris due to coronary artery spasm and chronic stable angina.

## **Dosage and administration**

Initially 30 mg three to four times daily increasing to 240 mg daily in divided doses. The maximum recommended dose is 360 mg daily.

### **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.

### **Impaired hepatic or renal function**

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

### **Concomitant use with other cardiovascular agents**

Sublingual glyceryl trinitrate may be taken as required to abort acute anginal attacks during Dilzem therapy.

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

## Contraindications

DILZEM is contraindicated in:

Patients with sick-sinus syndrome except in the presence of a functioning ventricular pace-maker.  
Patients with second or third degree AV block.  
Patients with hypotension (< 90mmHg systolic).  
Severe congestive heart failure or bradycardia.  
Idiosyncrasy to diltiazem.  
Pregnancy.

## Warnings and precautions

*Cardiac Conduction:* Caution is required in cases of first degree AV block. Diltiazem prolongs AV node refractory periods but not sinus node recovery times (except in sick sinus syndrome). This may result in slowing of heart rate, prolongation of the PR interval or even second or third degree AV block. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.

*Congestive Heart Failure:* Caution must be exercised in patients with congestive heart failure.

*Hypotension:* Arteriolar dilation produced by diltiazem administration may occasionally give rise to symptomatic hypotension.

*Acute Hepatic Injury:* In rare instances, patients receiving diltiazem have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes.

*Use in Pregnancy:* (Category C. Prescribing Medicines in Pregnancy 4<sup>th</sup> Ed. Australia). There are no well-controlled studies of the use of diltiazem HCl in pregnant women. There is the potential to produce foetal hypoxia associated with maternal hypotension therefore, diltiazem HCl should only be used if the potential benefit justifies the potential risk to the foetus.

*Use in Lactation:* Diltiazem HCl is excreted in human milk and breast milk concentrations may approximate serum levels. Since the safety and effectiveness of diltiazem HCl in infants and children has not been established an alternative method of infant feeding should be instituted if use of diltiazem HCl is deemed essential.

*Concomitant Administration with Beta-Blockers:* Diltiazem may cause marked prolongation of atrioventricular conduction in a small number of patients, and caution is advised if combination therapy is considered due to the risk of bradycardia. Such a combination should not be used in patients with depressed left ventricular function and conduction system disease.

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

*Use in Diabetics:* Diltiazem influences insulin secretion and peripheral action as a result of inhibition of calcium influx into cells so caution is required if diltiazem is considered for use in diabetic patients.

*Use with Amiodarone:* Caution is required if consideration is being given to the use of diltiazem and amiodarone in combination especially in the presence of underlying dysfunction of the sinus node such as bradycardia, sick sinus syndrome or partial AV block.

*Concomitant Use with Digoxin:* The combination of diltiazem with digitalis may give rise to additive effects in prolonging AV conduction.

*General:* Diltiazem is extensively metabolised by the liver, metabolites being eliminated by the kidneys and in bile. It should be used with caution & in reduced dosage in patients with impaired renal or hepatic function. Liver function tests should be monitored during prolonged use as very rare transaminase elevations have been noted.

Animal subacute toxicity and chronic toxicity studies in dogs and rats indicated hepatic damage occurred at high dosages. Such damage was reversible when the drug was discontinued.

Reproduction studies in mice, rats and rabbits showed administration of high doses resulted in embryo and foetal deaths. Skeletal abnormalities were also observed. Peri-natal and post-natal studies showed reduction in pup weights and survival rates with an increased incidence of still births.

Use of diltiazem is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

## **Adverse effects**

Side effects are rare. The most common occurrences are: gastrointestinal discomfort with nausea and vomiting, swelling and oedema, arrhythmia, headache and dizziness, rash and fatigue. Mild to moderate elevation of alkaline phosphatase and transaminases occurs rarely.

The committee on safety of medicines in the U.K. has noted the following adverse effects: serious skin reactions (exfoliative dermatitis and epidermal necrolysis), hypotension and one case of agranulocytosis. Bradycardia and heartblock (sinoatrial &/or atrioventricular) have also been noted as have muscular (including myalgia) effects and ocular (including abnormal vision) changes.

Atrioventricular block is an uncommon but potentially serious adverse effect of diltiazem treatment and the risk is increased by concurrent use of a beta-blocker.

## **Interactions**

The combination of diltiazem with beta-blockers may produce a positive clinical response in patients with angina pectoris. Care is required, however, since AV conduction may be prolonged leading to serious deleterious effects (See Warnings and Precautions). Diltiazem is known to modify digoxin pharmacokinetics in healthy subjects, and in patients with cardiac insufficiency or chronic atrial fibrillation.

These modifications involved: an increase in plasma digoxin concentration of 24-70%, a decrease in mean renal digoxin clearance from 86.9 mL/min to 62.8 mL/min, and an increase in the mean digoxin elimination half-life from 36.7 h to 44.5 h.

Concurrent administration of diltiazem with cimetidine results in an increase in both diltiazem and desacetyl diltiazem plasma levels. Concomitant administration of diltiazem with diazepam causes a significant decrease, averaging between 20-30%, in diltiazem plasma levels. The combination of diltiazem with amiodarone may have additive adverse effects on sinus node function and myocardial contractility.

Chronic administration of diltiazem to patients on cyclosporin-A will result in increased trough levels of cyclosporin-A.

Diltiazem HCl should not be administered with carbamazepine as two well-documented cases have been reported where combination resulted in neurotoxicity.

A single case has been reported of cardiac arrhythmia involving sinus arrest and impaired AV conduction after administration of enflurane and diltiazem together.

A single case has been reported of decreased insulin effect after combination treatment of insulin and diltiazem although the mechanism was not established.

Concurrent use of diltiazem and sustained-release nitroglycerin preparations is to be avoided.

Care should be exercised initially if it is necessary to coadminister diltiazem and theophylline due to possible toxicity.

Ingestion of grapefruit has been shown to increase the half-life of diltiazem as a result of inhibition of gut wall metabolism of diltiazem during absorption. The clinical significance of this is unknown. It is recommended that ingestion of grapefruit or grapefruit juice be avoided, or at least do not take grapefruit/grapefruit juice within 10 hours before or two hours after taking diltiazem 30 mg and 60 mg tablets.

Patients on diltiazem treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. This is thought to be mediated through diltiazem inhibition of Cytochrome P 450 3A4 enzymes and the P-glycoprotein drug transporter leading to increased simvastatin plasma levels. The risk of myopathy is approximately 1% in these patients. Treatment with simvastatin in a patient taking diltiazem hydrochloride should be started at the lowest possible dose and titrated upwards. If diltiazem hydrochloride treatment is to be added to patients already taking simvastatin, consider a reduction in statin dose and retitrate against serum cholesterol concentrations.

## 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 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

## **Pharmaceutical precautions**

36 months from date of manufacture stored at or below 25°C. Protect from light and moisture. Keep out of reach of children.

## **Medicine classification**

Prescription Medicine.

## **Package quantities**

Bottles of 100 tablets. Blister packs of 30 tablets.

## **Further information**

The active ingredient of DILZEM, diltiazem hydrochloride, is CIS-(+)-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxy-phenyl)-5,5-benzothiazepin-4(5H)-one hydrochloride. Its molecular formula and weight are  $C_{22}H_{26}N_2O_4S.HCl$  and 451 respectively.

Other ingredients are:

Lactose, Cutina HR, Aluminium hydroxide gel dried, Eudragit NE30D, Talc, and Magnesium stearate for the core and Opadry white (Y-IR-7000B) for coating.

The oral  $LD_{50}$  in mice and rats ranges from 415-740 mg/kg and 560-810 mg/kg respectively. The intravenous  $LD_{50}$  in both species is 60 mg/kg and 38 mg/kg respectively. The oral  $LD_{50}$  in dogs is considered to be in excess of 50 mg/kg. Lethality in monkeys was seen at 360 mg/kg. The toxic dose in man is unknown, but blood levels in excess of 800 ng/mL have not been associated with toxicity.

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