

# NEW ZEALAND DATASHEET

## Diltahexal

*Diltiazem Hydrochloride Ph Eur, film coated tablet, 60 mg*

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### Presentation

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White, 9 mm, film-coated tablets, scored on one side. Each tablet contains diltiazem hydrochloride 60 mg. This product is not able to deliver all approved dose regimes. Do not halve tablet.

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### Uses

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#### **Actions**

##### **Pharmacotherapeutic group**

C08DB01 - Selective calcium channel blockers with mainly vascular effects, benzothiazepine derivatives, diltiazem.

##### **Mechanism of action**

Diltiazem, a benzothiazepine type calcium antagonist, inhibits calcium ion entry into smooth muscle cells by blockade of slow calcium channels. Diltiazem acts as a potent coronary vasodilator and also has a moderate effect on peripheral circulation. Diltiazem may also prolong AV nodal conduction.

##### **Pharmacodynamic effects**

The therapeutic effects 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.

Diltiazem produces its antihypertensive effects by primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure 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 normotensives.

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

In man diltiazem hydrochloride 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 end diastolic pressure have not been affected. Increased heart rate has however been reported in occasional patients with pre-existing impairment of the ventricular function. There is very little data on the interaction of diltiazem hydrochloride and beta-blockers in patients with

poor ventricular function. Resting heart rate is usually 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 increases activity of the renin-angiotension-aldosterone axis has been observed. Diltiazem antagonises the renal and peripheral effects of angiotension 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.

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.

#### *Clinical studies*

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs atrial-His conduction time and atrioventricular node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of diltiazem 300 mg in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first degree atrioventricular block. Diltiazem associated prolongation of the atrial-His interval is not more pronounced in patients with first degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of Diltiazem in doses of up to 240 mg/day has resulted in small increases in PK interval but has not usually produced abnormal prolongation. There were, however, three instances of second degree atrioventricular block and one instance of third degree atrioventricular block in a group of 959 chronically treated patients.

### **Therapeutics**

#### *Angina due to coronary artery spasm (vasospastic angina)*

Diltiazem has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. and it inhibits spontaneous and ergometrine induced coronary artery spasm.

#### *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 through reductions in heart rate, systemic blood pressure at submaximal and maximal exercise work loads and dilation of coronary arteries.

### **Pharmacokinetics**

#### **Absorption**

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 to 60 minutes after administration, peak levels are normally achieved 2 to 4 hours after administration of the 60 mg tablets.

#### **Distribution**

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 to 86% of plasma diltiazem, 35 to 40% being bound to albumin and the rest to alpha-glycoprotein. Competitive ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid or warfarin. Diltiazem hydrochloride is excreted in breast milk.

## **Biotransformation**

Diltiazem is extensively metabolised in the liver by deacetylation, N-demethylation and O-demethylation such that only 0.1 to 4% of unchanged diltiazem appears in the urine. Five metabolites have been identified. Desacetyldiltiazem is normally present in plasma at levels of 10 to 20% of the parent medicine and is 25 to 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 drug. The other metabolites are devoid of pharmacological activity.

## **Elimination**

Studies in rats have shown that after administration of <sup>14</sup>C-diltiazem, greater than 90% of the <sup>14</sup>C label 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 elimination half-life following single or multiple drug administration is approximately 4 to 6 hours.

## **Correlation with therapeutic activity**

Therapeutic blood levels of diltiazem appear to be in the range of 50 to 200 nanogram/ml. Plasma levels above 50 ng/ml are achieved between 1 to 1.5 hours and are maintained for approximately 8 hours after administration of the 60 mg tablets. 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. 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.

## **Special patient considerations**

### *Patients with hepatic or renal impairment*

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.

## **Indications**

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

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## **Dosage and administration**

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This product is not able to deliver all approved dose regimes. Do not halve tablet.

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

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## Contraindications

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Known hypersensitivity to diltiazem or to any of the inactive ingredients listed in [Further information](#).

Sick-sinus syndrome except in the presence of a functioning ventricular pace-maker; sinoatrial (SA) node disorders; second or third degree atrioventricular block except in the presence of a functioning ventricular pacemaker; hypotension (< 90 mmHg systolic); severe congestive heart failure; severe bradycardia (below 40 bpm); left ventricular failure with pulmonary congestion; patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission; idiosyncrasy or hypertension to diltiazem; concomitant use of dantrolene infusion (refer to [Interactions](#)); Pregnancy.

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## Warnings and precautions

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### Warnings

#### Cardiac conduction

Close observation is necessary in patients with reduced left ventricular function, bradycardia or with a first degree AV block. Diltiazem prolongs A-V 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 prolongation of the PR interval or even second- or third-degree A-V block (6 of 1,243 patients, or 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem hydrochloride.

#### 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 decrease in contractile function (dp/dt). Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

#### Hypotension

Arteriolar dilation with consequential decreases in blood pressure is associated with diltiazem therapy and 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 such as alkaline phosphatase, LDH, SGOT, SGPT, 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 (refer to [Adverse effects](#)).

#### Concomitant administration with beta-blockers

Controlled and uncontrolled studies suggest that the concomitant use of diltiazem and beta-blockers or digitalis glycosides is usually well tolerated. However, 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 (refer to [Interactions](#)).

#### Abrupt withdrawal

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

## ***Precautions***

### **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, metabolites being eliminated by the kidneys and in bile. Diltiazem should be used with caution and at 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.

### **Use in diabetics**

Diltiazem should be used with caution in patients suffering from diabetes. In common with 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' 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 A-V block (refer to [Interactions](#)).

### **Concomitant use with digoxin**

Diltiazem has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics (refer to [Interactions](#)). 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. The combination of diltiazem with digoxin or digitalis glycosides may have additive effects in prolonging AV conduction. 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 diltiazem treatment longer than one year with doses higher than 240 mg/day are limited. Therefore long-term treatment with doses exceeding 240 mg/day is not recommended.

### **Use in the elderly**

Administration of diltiazem to elderly patients 65 years of age or older 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.

### **Paediatric use**

Safety and effectiveness in children have not been established.

### **Lactose intolerance**

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## ***Pregnancy and lactation***

### **Use in pregnancy**

Assigned Category C by the Australian Drug Evaluation Committee. This category includes medicines 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 texts should be consulted for further details.

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. In common with other calcium channel blockers, diltiazem has the potential to produce 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**

Residual diltiazem may be present in breast milk at levels corresponding to approximately 0.9% of the maternal dose. Diltiazem is considered unlikely to be problematical in breastfeeding.

#### ***Effects on ability to drive and use machines***

This medicine is presumed to be safe or unlikely to produce an effect.

#### ***Other***

##### **Preclinical safety data**

###### *Toxicology*

The oral LD50 values in mice and rats ranged from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD50 values in these species were 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 unknown, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

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#### **Adverse effects**

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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.

##### ***Common reactions***

In clinical trials of diltiazem in anginal patients, the most common events (i.e. greater than 1%) were oedema (2.4%), headache (2.1%), nausea (1.9%), atrioventricular block (1.5%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), urticaria and light headedness.

##### ***Uncommon reactions***

The following events were reported infrequently (less than 1%).

###### **Cardiovascular**

Angina, arrhythmia, first degree atrioventricular block, second- or third-degree atrioventricular block, bradycardia, bundle branch block, congestive heart failure, ECG abnormalities, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles. 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.

###### **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, thirst, vomiting, weight increase, mild elevations of SGOT, SGPT, AST, ALT, LDH, and alkaline phosphatase. In rare cases, clinical hepatitis has been reported, reversible upon discontinuation of diltiazem.

## **Dermatological**

Petechiae, photosensitivity, pruritus, urticaria.

## **Other**

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

## **Post-marketing surveillance**

The following post-marketing events have been reported infrequently in patients receiving diltiazem: alopecia, gynaecomastia, vasculitis, musculo-cutaneous reactions such as simple erythema or occasionally desquamative erythema with or without fever, angioneurotic oedema, symptoms of vasodilation (such as flushing, lower limb oedema, sweating), erythema multiforme (including rare cases of Stevens-Johnson syndrome), acute generalised exanthematous pustular dermatitis, sino-atrial block, orthostatic hypotension, malaise, gastric pain, purpura, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, haemolytic anaemia, increased bleeding time, leucopenia, retinopathy, agranulocytosis and thrombocytopenia. Bradycardia and heart block (sino-atrial and/or atrioventricular) have also been noted as have muscular (including myalgia) effects and ocular (including abnormal vision) changes. Very rare cases of toxic epidermal necrolysis have 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 leucocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

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## **Interactions**

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### ***Medicines and other pharmacologically active substances***

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 undergoes biotransformation by cytochrome P450 mixed function oxidase. Co-administration of diltiazem with other agents that follow the same route of biotransformation may result in the competitive inhibition or induction of metabolism. This may lead to an increased risk of adverse reactions.

### **Alpha-adrenoceptor antagonists**

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 (refer to Warnings and precautions).

### **Anaesthetic agents**

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

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

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

### **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.

### **Beta-blockers**

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 (refer to Warnings and precautions).

Controlled and uncontrolled studies suggest that concomitant use of diltiazem and beta-blockers or digitalis glycosides 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.

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.

Due to the possibility of rhythm disturbances, combination therapy with diltiazem and beta-blockers must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

### **Carbamazepine**

Two well-documented cases have been reported where the combination of diltiazem with carbamazepine resulted in neurotoxicity. 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.

### **Cyclosporin**

Chronic administration of diltiazem to patients on cyclosporin has resulted in increased trough levels of cyclosporin 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.

### **Dantrolene infusion**

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

### **Diazepam**

Diazepam has been reported to cause a significant decrease in diltiazem plasma levels. The average decrease in diltiazem concentration was between 20 and 30%. Three out of eight patients showed decreases which were greater than 50%.

### **Digoxin**

Concomitant use of diltiazem and digoxin may result in an additive effect on conduction. Diltiazem is known to modify digoxin pharmacokinetics in healthy subjects, in patients with cardiac insufficiency and in patients with chronic atrial fibrillation. The following effects were noted during conventional diltiazem co-administration: increases in plasma digoxin concentrations ranged from 24 to 70%; the renal digoxin clearance decreased from 86.9 to 62.8 ml/minute; digoxin elimination half-life was prolonged from 36.7 to 44.5 hours. 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 receptor antagonists**

Concomitant use may result in increased plasma diltiazem concentrations. Patients receiving diltiazem concurrently with a H2 receptor antagonist should be carefully monitored when initiating or discontinuing therapy with the H2 receptor antagonist. An adjustment in the daily dose of diltiazem may be necessary.

Concurrent administration of diltiazem with cimetidine produced an increase in the plasma levels of single-dose diltiazem approximately 50% over control and its metabolite desacetyldiltiazem.

### **Insulin**

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

### **Lithium**

There is an increased risk of lithium-induced neurotoxicity.

### **Organic nitrates - short and long acting**

Increased hypotensive effects and faintness may be seen due to additive vasodilating effects. In patients treated with calcium antagonists, the addition of nitrate derivatives should only be carried out gradually, increasing doses. Concurrent use of diltiazem and sustained-release glyceryl trinitrate preparations is to be avoided.

### **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.

### **Rimonabant**

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

### **Theophylline**

Concomitant use results in an increase in circulating theophylline levels. Care should be exercised initially if it is necessary to co-administer diltiazem and theophylline due to possible toxicity.

### **Simvastatin**

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 should be started at the lowest possible dose and titrated upwards. If diltiazem treatment is to be added to patients already taking simvastatin, consider a reduction in statin dose and re-titrate against serum cholesterol concentrations.

## ***Food and alcohol***

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.

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## **Overdosage**

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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. 16 of these reports involved multiple drug ingestions. 22 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.

## ***Signs and symptoms***

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.

## ***Management***

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

### **Bradycardia**

Administer atropine (0.60 to 1.0 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 (e.g. isoprenaline, dopamine, or dobutamine) and diuretics.

### **Hypotension**

Administer vasopressors (e.g. dopamine or noradrenaline acid tartrate).

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

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## Pharmaceutical precautions

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### ***Instructions for use/handling***

Nil.

### ***Incompatibilities***

None known.

### ***Special precautions for storage***

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

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## Medicine classification

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Prescription Medicine

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## Package quantities

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Packs of 90 tablets in cartoned blister strips.

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## Further information

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### ***List of excipients***

Microcrystalline cellulose, lactose, hydrogenated castor oil, povidone, polyethylene glycol, sodium starch glycolate, silicon dioxide, magnesium stearate, hydroxypropylmethylcellulose, stearic acid, titanium dioxide.

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## Name and address

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Novartis New Zealand Limited  
Private Bag 65904 Mairangi Bay  
AUCKLAND 0754

Telephone: (09) 361 8100

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## Date of preparation

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21 January 2010