



APO-DILTIAZEM CD

1. APO-DILTIAZEM CD (120mg, 180mg, 240mg and 300mg controlled release capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diltiazem hydrochloride 120mg

Diltiazem hydrochloride 180mg

Diltiazem hydrochloride 240mg

Diltiazem hydrochloride 300mg

Excipient with known effect

Apo Diltiazem CD is gluten and lactose free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-DILTIAZEM CD 120mg capsules are size 2 gelatin capsules with a light turquoise body and light turquoise cap, imprinted APO 120. Each capsule contains 120mg diltiazem hydrochloride and typically weighs 244mg.

APO-DILTIAZEM CD 180mg capsules are size 1 gelatin capsules with a light turquoise body and light blue cap, imprinted APO 180. Each capsule contains 180mg diltiazem hydrochloride and typically weighs 350mg.

APO-DILTIAZEM CD 240mg capsules are size 0 gelatin capsules with a light blue body and light blue cap, imprinted APO 240. Each capsule contains 240mg diltiazem hydrochloride and typically weighs 460mg.

APO-DILTIAZEM CD 300mg capsules are size 0 elongated capsules with a light grey body and light blue cap, imprinted APO 300. Each capsule contains 300mg diltiazem hydrochloride and typically weighs 562mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APO-DILTIAZEM CD is indicated for the treatment of hypertension either alone or in combination with other antihypertensive agents such as diuretics.

APO-DILTIAZEM CD is also indicated for the management of chronic stable angina and angina resulting from coronary artery spasm.

4.2 Dose and method of administration

Patients controlled on diltiazem alone or in combination with other medications may be safely switched to APO-DILTIAZEM CD capsules 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



APO-DILTIAZEM CD

clinical experience with doses above 360mg. Therefore, treatment with doses exceeding 360mg/day is not recommended.

Adults

Hypertension

Dosage needs to be adjusted by titration according to individual patient needs. When used as monotherapy reasonable starting doses are 180 to 240mg 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 360mg daily.

Angina

Dosages for the treatment of angina should be adjusted to each patient's needs starting with a dose of 120 or 180mg once daily. Individual patients may respond to higher doses of up to 360mg 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 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 Section 4.4 Special warnings and precautions for use)

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 impairments. If diltiazem must be used in these patients, the dosage should be carefully and gradually adjusted depending on patient tolerability and responses (see Section 4.4 Special warnings and precautions for use)

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 both short and long acting nitrates.

Beta-blockers (see Section 4.4 special warnings and precautions for use).

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

Paediatric Population

Safety and effectiveness in children have not been established. Therefore APO-DILTIAZEM CD is not recommended for use in children.

Method of administration

For oral administration

4.3 Contraindications

APO-DILTIAZEM CD is contraindicated in patients with:

- 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 mm Hg systolic)
- Congestive heart failure
- Severe bradycardia (below 40 bpm)
- Concomitant use of dantrolene infusion (see Section 4.5 Interaction with other medicines and other forms of interaction)
- Concomitant use of ivabradine (see Section 4.5 Interaction with other medicines and other forms of interactions)
- Hypersensitivity or idiosyncrasy to diltiazem or any of the excipients stated in Section 6.1 List of excipients
- Breastfeeding
- Left ventricular failure with pulmonary congestion
- Acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

4.4 Special warnings and precautions for use

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression (see Section 4.5 Interaction with other medicines and other forms of interaction and Section 4.8 Undesirable effects. 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).

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second or third-degree AV block (9 of 2,111 patients, or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction (see Section 4.5 Interaction with other medicines and other forms of interactions). A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60mg 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 (see Section 4.5 Interaction with other medicines and other forms of interactions).

Hypotension

Decreases in blood pressure associated with diltiazem therapy may 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, AST, 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 Section 4.8 Undesirable effects).

Dermatological Events

Dermatological events (see Section 4.8 Undesirable effects) may be transient and may disappear despite continued use of diltiazem. 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 2 to 6 months of diltiazem administration. Careful monitoring is necessary in patients with latent or manifested diabetes mellitus due to a possible increase in blood glucose.

Respiratory Events

The use of diltiazem may induce bronchospasm, including asthma aggravation, especially in patients with pre-existing bronchial hyper-reactivity. Cases have also been reported after dose increase. Patients should be monitored for signs and symptoms of respiratory impairment during diltiazem therapy.

Concomitant Administration with Beta-blockers

Controlled and uncontrolled studies suggest that concomitant use of diltiazem 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 Section 4.5 Interactions with other medicines and other forms of interactions).

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.

Use with Amiodarone

Amiodarone should be used with caution with diltiazem particularly if there is suspicion of underlying dysfunction of the sinus node, such as bradycardia or sick sinus syndrome or if there is partial AV block (see Section 4.5 Interactions with other medicines and other forms of interactions).

Concomitant Use of Digoxin

Diltiazem has been shown to increase serum digoxin concentrations and to modify its pharmacokinetics (see Section 4.5 Interactions with other medicines and other forms of interactions). Patients with plasma digoxin levels in the upper therapeutic range (1.5 to 2.5ng/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 or with doses higher than 360mg/day are limited. Treatment at doses above 360mg/day does not offer increased efficacy, but is associated with a greater risk of adverse reactions. Therefore treatment with doses exceeding 360mg/day is not recommended.

Abrupt Withdrawal

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

Use in Hepatic or Renal Impairment

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 close monitoring particularly of heart rate, should be carried out at the beginning of treatment.

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. APO-DILTIAZEM CD 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 diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral studies of 125mg/kg and higher in rates were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Use in Children

Safety and effectiveness in children have not been established. Therefore APO-DILTIAZEM CD is not recommended for use in children.

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.

Effects on laboratory tests No data available

4.5 Interaction with other medicines and other forms of interaction

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.

Diltiazem is metabolised by CYP3A4. A moderate (less than 2-fold) increase in 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 in diltiazem plasma concentrations.

No pharmacokinetic interaction studies have been conducted with diltiazem CD or SR formulations. However, interactions reported with the conventional formulation are still relevant. As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition or induction for 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 they 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.

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.

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.

Beta-blockers

Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-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.

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.

An increased risk of depression has been reported when diltiazem is co-administered with beta-blockers (see Section 4.8 Undesirable effects)

Digoxin

Concomitant use of diltiazem and digoxin may result in 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 co-administration. There is an increased risk of bradycardia with this combination. Caution is required when digoxin is combined with diltiazem, particularly in the elderly and when high doses are used.

H₂ antagonists (cimetidine, ranitidine)

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

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

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%.

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.

Phenytoin

When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration. It is recommended that phenytoin plasma concentrations be monitored.

Lithium

There is an increased risk of lithium-induced neurotoxicity.

Theophylline

Concomitant use results in an increase in circulating theophylline levels.

Ivabradine

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem (see Section 4.3 Contraindications)

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 myocardial contractility (see Section 4.4 Warnings and 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 is due to statins metabolized 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 20mg dose of simvastatin in 10 healthy volunteers, after 2 weeks of 120mg diltiazem CD capsules 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 of diltiazem with simvastatin should be used with caution, particularly at the higher end of the dosing range.

In another 10 volunteer study, the co-administration of 120mg diltiazem SR capsules 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} were observed during diltiazem SR capsules co-administration.

The effects of statins on the pharmacokinetic parameters of diltiazem have not been determined.

Cilostazol

Concomitant administration has resulted in the inhibition of cilostazol metabolism (CYP3A4). Diltiazem has been shown to increase cilostazol exposure and to enhance its pharmacological activity.

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.

Asiprin/Acetylsalicylates

The concomitant administration of aspirin/acetylsalicylates with diltiazem should be undertaken with caution because of the increased risk of bleeding due to potential additive effect on platelet aggregation.

Other Antiplatelet Drugs

In a pharmacological study, diltiazem was shown to inhibit platelet aggregation. Although the clinical significance of this finding is unknown, potential additive effects when used with antiplatelet drugs should be considered.

Grapefruit Juice

Grapefruit juice may increase diltiazem exposure. Patients who consume grapefruit juice should be monitored for increased effects of diltiazem. Grapefruit should be avoided if an interaction is suspected.

X-ray Contract Media

Cardiovascular effects of an intravenous bolus of an ionic x-ray contract media, such as hypotension, may be increased in patients treated with diltiazem. Special caution is required in patients who concomitantly receive diltiazem and x-ray contrast media.

4.6 Fertility, pregnancy and lactation

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 prenatal/postnatal studies where 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 for foetal hypoxia associated with maternal hypotension. Diltiazem is therefore not recommended during pregnancy, as well as in women of child bearing potential not using effective contraception.

Breast-feeding

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, 60mg four times a day. The peak level in milk was as high as 200ng/ml and was almost the same as that in the serum. These data show that diltiazem is freely diffusible in milk but it is not known whether it is harmful to the newborn. Therefore,

breastfeeding while taking this drug should be avoided. If use of diltiazem is considered medically essential, an alternate method of infant feeding should be instituted.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

On the basis of reported adverse drug reactions, patients should be warned about the potential for i.e. dizziness (common), malaise (common) could alter the ability to drive or operate machinery and should be advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known. However, no studies have been performed. APO-DILTIAZEM CD is likely to produce minor or moderate adverse effects on the ability to drive or use machinery

4.8 Undesirable 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.

The following table presents the most common adverse reactions reported in placebo- controlled angina and hypertension trials in patients receiving diltiazem as CD capsules up to 360mg with rates in placebo patients shown for comparison.

Table 1 DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION AND ANGINA TRIALS (with the CD formulation)

ADVERSE REACTION	DILTIAZEM (CD formulation) N = 607	PLACEBO N = 301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV block first degree	3.3%	--
Oedema	2.6%	1.3%
ECG abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of diltiazem as CD capsules, tablets and SR capsules involving 3,200 patients the following undesirable effects were reported. They are presented in Table 2 by system organ class (SOC) and ranked under heading of frequency.

The following CIOMS frequency rating is used:

Very common: $\geq 10\%$; Common: ≥ 1 and $< 10\%$; Uncommon: ≥ 0.1 and $< 1\%$; Rare: ≥ 0.01 and $< 0.1\%$; Very rare: $< 0.01\%$; Not known: cannot be estimated from available data.

Table 2 REPORTED UNDESIRABLE EFFECTS IN THE SYSTEM ORGAN CLASS FORMAT.

System Organ Class	Frequency and Symptom
Metabolism and nutritional disorders	Uncommon: hyperglycaemia, hyperuricemia
Nervous system disorders	Common: headache (4.9%), Dizziness (3.5%), asthenia (2.7%)

	Uncommon: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality change, somnolence, tinnitus, tremor
Eye disorders	Uncommon: Amblyopia, eye irritation
Cardiac disorders	Common: first degree AV block (2.2%), second or third degree AV block, bradycardia (1.6%), palpitations
	Uncommon: Angina, arrhythmia, bundle branch block, congestive heart failure, ECG abnormalities, hypotension, syncope, tachycardia, ventricular extrasystoles
Vascular disorders	Common: flushing (1.5%)
	Uncommon: orthostatic hypotension
Respiratory disorders	Uncommon: dyspnoea
Gastrointestinal disorders	Common: nausea (1.4%), dyspepsia (1.2%), constipation, gastric pain,
	Uncommon: anorexia, diarrhoea, dry mouth, dysgeusia, thirst, vomiting, weight increase
Hepato-biliary disorders	Uncommon: hepatic enzyme increase (AST, ALT, LDH, ALP), (in rare cases clinical hepatitis has been reported, reversible upon discontinuation of diltiazem; see Section 4.4 Special warnings and precautions for use),
Skin and subcutaneous tissue disorders	Common: rash (1.3%), erythema
	Uncommon: Petechiae, photosensitivity, pruritus, urticarial
Musculoskeletal and connective tissue disorders	Uncommon: CPK increase, muscle cramp, osteoarticular pain
Renal and urinary disorders	Uncommon: nocturia, polyuria
Reproductive system and breast disorders	Uncommon: impotence, sexual difficulties
General disorders and administration site conditions	Very Common: lower limb oedema
	Common: oedema (4.6%), malaise
	Uncommon: epistaxis, nasal congestion.

Post-Marketing Experience

The following post marketing events have been reported infrequently in patients receiving diltiazem: mood changes, (including depression), hyperglycaemia, extrapyramidal syndrome, sino-atrial block, congestive heart failure, sinus arrest, cardiac arrest (asystole), 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 or pustulosis , , 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 is yet to be established. Bronchospasm (including asthma aggravation) has also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

The oral LD₅₀ in mice and rats ranged from 415 to 740mg/kg and from 560 to 810mg/kg, respectively. The intravenous LD₅₀ in these species was 60 and 38mg/kg, respectively. The oral LD₅₀ in dogs is considered to be in excess of 50mg/kg, while lethality was seen in monkeys at 360mg/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 1g to 10.8g. Sixteen of these reports involved multiple drug ingestions. Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1g to 10.8g. 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, sinus arrest, cardiac arrest, 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 ventilator 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 1.0mg). If there is no response to vagal blockade administer isoprenaline cautiously.

High Degree AV Block

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

Cardiac failure

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

Hypotension

Vasopressors (e.g. dopamine or noradrenaline acid tartrate). Actual treatment and dosage should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

Symptoms and signs of overdose may be delayed due to the controlled release properties of the product, so patients should be kept under observation for at least 24 hours.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

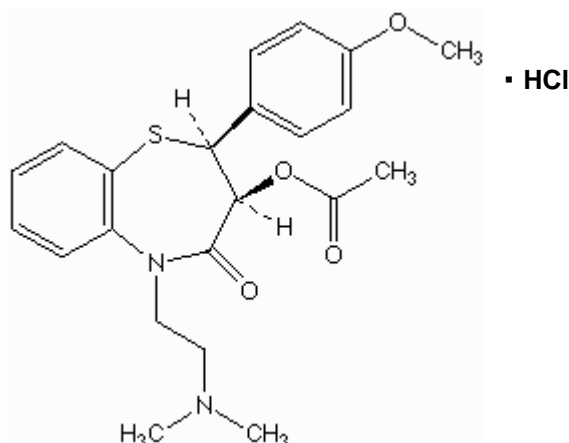
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Calcium channel blocker, Benzothiazepine derivatives

ATC code: C08DB01

Chemical Structure:



Molecular Formula: $\text{C}_{22}\text{H}_{26}\text{N}_2\text{S}\cdot\text{HCl}$

CAS number: 33286-22-5

Molecular weight: 450.98.

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

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.

Mechanism of Action

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.

Diltiazem hydrochloride produces its antihypertensive effects primarily by relaxation of the 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 normotensives.

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 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. Increase 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 beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

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

Chronic oral administration of diltiazem hydrochloride to patients in doses up to 540mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation (see Section 4.4 Special warnings and precautions for use)

5.2 Pharmacokinetic properties

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first- pass effect giving absolute bioavailability (compared to intravenous dosing) of approximately 40%. Diltiazem undergoes extensive metabolism in which 2-4% 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 shows diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid or warfarin. The plasma elimination half-life following single and multiple drug administration is approximately 3.0 to 4.5 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 therapeutic plasma levels of diltiazem appear to be in the range of 50-200 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 gastro intestinal 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.

When compared to a regimen of diltiazem tablets at steady state, more than 95% of drug is absorbed from the controlled delivery formulation. A single, 360mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours.

When diltiazem CD was co-administered with a high fat content breakfast the absorption of diltiazem was delayed but the extent of diltiazem absorption and total bioavailability were not affected. . Dose dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with the conventional tablets and SR tablets is observed. As the dose of diltiazem controlled delivery capsules is increased from a daily dose of 120mg to 240mg, there is an increase in the area- under-the curve of 2.7 times. When the dose is increased from 240mg to 360mg there is an increase in the area-under-the curve of 1.6 times.

No information is available regarding the pharmacokinetics and bioavailability of diltiazem in the CD or SR capsule form in patients with hepatic or renal failure, or in elderly hypertensive patients.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-DILTIAZEM CD 120mg, 180mg and 240mg capsules contain the following inactive ingredients:

- Methylcellulose
- microcrystalline cellulose
- tributyl citrate
- polysorbate
- purified talc
- methacrylic acid copolymer
- gelatin capsule shell (contains brilliant blue FCF and titanium dioxide as colouring agents)

APO-DILTIAZEM CD 300mg capsules contain the following inactive ingredients:

- Methylcellulose
- microcrystalline cellulose
- tributyl citrate

- polysorbate
- purified talc
- methacrylic acid copolymer
- gelatin capsule shell (contains brilliant blue FCF, ferric oxide (black) and titanium dioxide as colouring agents).

APO-DILTIAZEM CD capsules are lactose and gluten free.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from date of manufacture

6.4 Special Precautions

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

6.5 Nature and contents of container

APO-DILTIAZEM 120mg, 180mg, 240mg and 300mg in HDPE bottles containing 100 or 500 capsules.

APO-DILTIAZEM 120mg, 180mg, 240mg and 300mg in PVC/PVDC or PVC/PE/PVDC blisters containing 100 capsules.

Not all pack sizes maybe marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Glenfield
AUCKLAND 0627

Telephone: (09) 444 2073

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APO-DILTIAZEM CD

E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

14 September 2000

10. DATE OF REVISION OF THE TEXT

13 September 2018

Summary Table of Changes

Section changed	Summary of new information
2, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6 & 10	Minor editorial changes
4.1, 4.2, 4.4, 4.5, 4.7, 4.8 & 4.9	Safety related updates