PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] DILTIAZEM CD

Diltiazem Hydrochloride Controlled Delivery Capsules

Controlled Delivery Capsules, 120 mg, 180 mg, 240 mg and 300 mg, Oral

Manufacturer's Standard

Antihypertensive Agent

Antianginal Agent

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	03/2026

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4

1.1 Pediatrics 4

1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

4 DOSAGE AND ADMINISTRATION 5

4.1 Dosing Considerations 5

4.2 Recommended Dose and Dosage Adjustment 5

4.4 Administration 6

4.5 Missed Dose 6

5 OVERDOSAGE 6

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 7

7 WARNINGS AND PRECAUTIONS 8

7.1 Special Populations 11

7.1.1 Pregnant Women 11

7.1.2 Breast-feeding 11

7.1.3 Pediatrics 11

7.1.4 Geriatrics 12

8 ADVERSE REACTIONS 12

8.1 Adverse Reaction Overview 12

8.2 Clinical Trial Adverse Reactions 12

8.5 Post-Market Adverse Reactions 15

9 DRUG INTERACTIONS 16

9.1 Serious Drug Interactions 16
9.2 Drug Interactions Overview 16
9.3 Drug-Behavioural Interactions 16
9.4 Drug-Drug Interactions 17
9.5 Drug-Food Interactions 24
9.6 Drug-Herb Interactions 25
9.7 Drug-Laboratory Test Interactions 25
10 CLINICAL PHARMACOLOGY 25
10.1 Mechanism of Action 25
10.2 Pharmacodynamics 26
10.3 Pharmacokinetics 26
11 STORAGE, STABILITY AND DISPOSAL 28
PART II: SCIENTIFIC INFORMATION 29
13 PHARMACEUTICAL INFORMATION 29
14 CLINICAL TRIALS 29
14.2 Comparative Bioavailability Studies 29
16 NON-CLINICAL TOXICOLOGY 33
17 SUPPORTING PRODUCT MONOGRAPHS 38
PATIENT MEDICATION INFORMATION 39

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DILTIAZEM CD (Diltiazem Hydrochloride) is indicated for:

Angina

DILTIAZEM CD is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic, despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. DILTIAZEM CD may be tried in combination with beta-blockers in chronic stable angina patients with normal ventricular function. When such concomitant therapy is introduced, patients must be monitored closely (see 7 WARNINGS AND PRECAUTIONS).

Hypertension

DILTIAZEM CD is indicated for the treatment of mild to moderate essential hypertension. Safety of concurrent use of diltiazem with other antihypertensive agents has not been established.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DILTIAZEM CD in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): 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 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

DILTIAZEM CD is contraindicated:

- In patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- In patients with second or third-degree AV block.
- In patients with known hypersensitivity to diltiazem or to any of the excipients.
- In patients with hypotension (less than 90 mm Hg systolic).
- In patients with severe bradycardia (below 40 beats per minute).
- In myocardial infarction patients, who have left ventricular failure manifested by pulmonary congestion.

- In pregnancy and in women of childbearing potential.
- Breast-feeding.
- With concomitant use of dantrolene infusion.
- With concomitant use of ivabradine.
- With concomitant use of lomitapide mesylate as it may result in increased concentrations of lomitapide mesylate due to CYP3A4 inhibition (see 9.4 Drug-Drug Interactions).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Geriatrics (see 4.2 Recommended Dose and Dose Adjustment and 7.1.4 Geriatrics).
- Renal disease (see 4.2 Recommended Dose and Dose Adjustment and 7 WARNINGS AND PRECAUTIONS).
- Hepatic disease (see 4.2 Recommended Dose and Dose Adjustment and 7 WARNINGS AND PRECAUTIONS).
- Rule out pregnancy (see 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women).
- Concomitant therapy with drugs metabolized by the CYP450 system (see 9.1 Serious Drug Interactions, 9.2 Drug Interactions Overview, and 9.4 Drug-Drug Interactions).

4.2 Recommended Dose and Dosage Adjustment

Angina

Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 360 mg once daily. When necessary, titration should be carried out over a 7 to 14-day period.

Patients controlled on diltiazem alone or in combination with other medications may be safely switched to 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 experience with doses above 360 mg, however, the incidence of adverse reactions increases as the dose increases with first degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose. Therefore, doses greater than 360 mg are not recommended.

Hypertension

Dosage should be individualized depending on patient's tolerance and responsiveness to DILTIAZEM CD capsules. When used as monotherapy, usual starting doses are 180 to 240 mg

once daily, although some patients may respond to 120 mg once daily. Maximum antihypertensive effect is usually observed after approximately 2 to 4 weeks of therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg once daily.

A maximum daily dose of 360 mg once daily should not be exceeded.

The dosage of DILTIAZEM CD or concomitant antihypertensive agents may need to be adjusted when adding one to the other.

See 7 WARNINGS AND PRECAUTIONS regarding use with beta-blockers.

Dosage in elderly patients

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 7 WARNINGS AND PRECAUTIONS).

There are few available data concerning dosage requirements in patients with impaired renal or hepatic function. If diltiazem must be used in these patients, the dosage should be carefully and gradually adjusted depending on patient tolerance and response (see 7 WARNINGS AND PRECAUTIONS).

4.4 Administration

DILTIAZEM CD capsules should not be chewed or crushed.

4.5 Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule.

5 OVERDOSAGE

There have been reports of diltiazem overdose in amounts ranging from < 1 g to 18 g. In cases with a fatal outcome, the majority involved multiple drug ingestion.

Events observed following diltiazem overdose included sinus bradycardia with or without isorhythmic dissociation, pronounced hypotension possibly leading to collapse, and acute kidney injury, sinus arrest, heart block, atrioventricular conduction disturbance, cardiac arrest, and cardiac failure.

The effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases, intravenous calcium has been administered (1 g calcium chloride or 3 g calcium gluconate) over 5 minutes and repeated every 10 to 20 minutes as necessary. Calcium gluconate has also been administrated as a continuous infusion at a rate of 2 g per hour for 10 hours.

Infusions of calcium for 24 hours or more may be required. Patients should be monitored for signs of hypercalcemia.

In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination. The following measures may be considered:

- **Bradycardia:** Administer atropine. If there is no response to vagal blockade, administer isoproterenol 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 (isoproterenol, dopamine or dobutamine) and diuretics.
- **Hypotension:** Administer fluids and vasopressors (e.g., dopamine or noradrenaline). Actual treatment and dosage should depend on the severity of the clinical situation.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 120 mg, 180 mg, 240 mg, 300 mg Diltiazem Hydrochloride	Eudragit, FD&C blue #1, gelatin, iron oxide black (300 mg only), methacrylic acid copolymer, methylcellulose, microcrystalline cellulose, polysorbate 80, talc, titanium dioxide and tributyl citrate.

Description

DILTIAZEM CD 120 mg: Light turquoise blue opaque body, light turquoise blue opaque cap, hard gelatin capsules, imprinted “APO 120”, with white spheroidal bead fill.

DILTIAZEM CD 180 mg: Light turquoise blue opaque body, light blue opaque cap, hard gelatin capsules, imprinted “APO 180”, with white spheroidal bead fill.

DILTIAZEM CD 240 mg: Light blue opaque body, light blue opaque cap, hard gelatin capsules, imprinted “APO 240”, with white spheroidal bead fill

DILTIAZEM CD 300 mg: Light grey opaque body, light blue opaque cap, hard gelatin capsules, imprinted “APO 300”, with white spheroidal bead fill.

Packaging

DILTIAZEM CD 120 mg, 180 mg, 240 mg and 300 mg capsules are supplied in bottles of 100 and 500 capsules.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac Conduction

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 (6 of 1208 patients or 0.5%).

First degree AV block was observed in 5.8% of patients receiving diltiazem (see 8 ADVERSE REACTIONS).

Concomitant use of diltiazem with agents known to affect cardiac conduction (such as beta-blockers, digitalis or amiodarone) may result in additive effects on cardiac conduction (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Prior to general anesthesia, the anesthetist must be informed of ongoing diltiazem treatment. Depression of cardiac contractility, conductivity, and automaticity, as well as the vascular dilatation associated with anesthetics may be potentiated by calcium channel blockers (see 9 DRUG INTERACTIONS).

Congestive Heart Failure

Because diltiazem has a negative inotropic effect *in vitro* and it affects cardiac conduction, the drug should only be used with caution and under careful medical supervision in patients with congestive cardiac failure (see 2 CONTRAINDICATIONS).

Hypotension

Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension. In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of diltiazem should be taken into consideration.

Use with Beta-blockers

The combination of diltiazem and beta-blockers warrants caution since in some patients additive effects on heart rate, AV conduction, blood pressure or left ventricular function have been observed. Close medical supervision is recommended.

Generally, diltiazem should not be given to patients with impaired left ventricular function while they receive beta-blockers. However, in exceptional cases when, in the opinion of the physician, concomitant use is considered essential, such use should be instituted gradually in a hospital setting.

Diltiazem gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Patients with Myocardial Infarction

Use of immediate release diltiazem at 240 mg per day started 3 to 15 days after a myocardial infarction was associated with an increase in cardiac events in patients with pulmonary congestion, and no overall effect on mortality. Although there has not been a study of diltiazem in acute myocardial infarction reported, their use may have effects similar to those of immediate release diltiazem in acute myocardial infarction.

Endocrine and metabolism

Patients with Diabetes

Careful monitoring is necessary to detect new onset of diabetes or in patients with diabetes mellitus (type 1 or type 2) due to an increase in blood glucose.

Gastrointestinal

Diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk of developing an intestinal obstruction.

Hepatic/biliary/pancreatic

Acute Hepatic Injury

In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury have been observed. These reactions have been reversible upon discontinuation of drug therapy. Although a causal relationship to diltiazem has not been established in all cases, a drug induced hypersensitivity reaction is suspected (see 8 ADVERSE REACTIONS). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

Impaired Hepatic Function

Diltiazem should be used with caution in patients with hepatic impairment. Because diltiazem is extensively metabolized by the liver and excreted in bile, the monitoring of laboratory parameters of hepatic function is recommended, and cautious dosage titration are recommended in patients with impaired hepatic function (see 8 ADVERSE REACTIONS).

Neurologic

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression (see 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS).

Renal

Acute Kidney Injury

Cases of acute renal failure have been reported in patients using diltiazem at therapeutic dosages. Patients at greater risk appear to have reduced left ventricular function, severe bradycardia, or severe hypotension.

Impaired Renal Function

Diltiazem should be used with caution in patients with renal impairment. Because diltiazem is excreted by the kidney, the monitoring of laboratory parameters of renal function is recommended, and cautious dosage titration are recommended in patients with impaired renal function (see 8 ADVERSE REACTIONS).

Respiratory

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

Skin

Dermatological events (see 8 ADVERSE REACTIONS) 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 dermatologic reaction persist, the drug should be discontinued.

7.1 Special Populations

7.1.1 Pregnant Women

DILTIAZEM CD is contraindicated in pregnancy and in women of child-bearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals. In repeated dose studies a high incidence of vertebral column malformations was present in the offspring of mice receiving more than 50 mg/kg of diltiazem HCl orally.

In the offspring of mice receiving a single oral dose of 50 or 100 mg/kg on day 12 of gestation, the incidence of cleft palate and malformed extremities was significantly higher. Vertebral malformations were most prevalent when they received the drug on day 9. In rats, a significantly higher fetal death rate was present when 200 and 400 mg/kg were given orally on days 9 to 14 of gestation. Single oral dose studies in rats resulted in a significant incidence of skeletal malformations in the offspring of the group receiving 400 mg/kg on day 11. In rabbits, all pregnant dams receiving 70 mg/kg orally from day 6-18 of gestation aborted; at 35 mg/kg, a significant increase in skeletal malformations was recorded in the offspring (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

Diltiazem has been reported to be excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. Since diltiazem safety in newborns has not been established, it should not be given to nursing mothers.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DILTIAZEM CD in pediatric patients has not been established; therefore,

Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include peripheral edema, bradycardia, palpitation, dizziness, rash, and polyuria. Therefore, particular care in titration is advisable (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Angina
In controlled trials, adverse events were reported in 21.1% of patients and required discontinuation in 2.2% of patients. The most common adverse effects reported were: first degree AV block (5.8%), dizziness (3.0%), headache (3.0%), asthenia (2.7%), bradycardia (2.5%), and angina pectoris (1.6%).

Hypertension
In controlled trials, adverse effects were reported in 30.7% of patients and required discontinuation of therapy in 2.1%. The most common adverse effects were headache (8.7%); edema (4.0%); bradycardia (3.7%); dizziness (3.4%), ECG abnormality (2.9%); asthenia (2.6%), and first-degree AV block (2.1%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

Angina

The safety of diltiazem hydrochloride controlled delivery capsules, administered at doses up to 360 mg a day, was evaluated in 365 patients with chronic stable angina treated in controlled and open-label clinical trials. Adverse events were reported in 21.1% of patients and required discontinuation in 2.2% of patients.

The most common adverse effects reported were: first degree AV block (5.8%), dizziness (3.0%), headache (3.0%), asthenia (2.7%), bradycardia (2.5%), and angina pectoris (1.6%).

The following percentage of adverse effects, divided by system, was reported:

Cardiovascular: First degree AV block (5.8%), bradycardia (2.5%), angina pectoris (1.6%), peripheral edema (1.4%), palpitations (1.1%), and ventricular extrasystoles (0.8%).

Central Nervous System: Dizziness (3.0%), headache (3.0%), asthenia (2.7%), insomnia (1.1%), nervousness (0.8%).

Dermatological: Rash (0.8%).

Gastrointestinal: Nausea (1.4%), diarrhea (0.5%).

Other: Amblyopia (0.5%).

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: bundle branch block, ventricular tachycardia, ECG abnormality, supraventricular extrasystoles, chest pain, syncope, postural hypotension, paresthesia, tremor, depression, mental confusion, impotence, abdominal pain, constipation, GI disorder, epistaxis, nuchal rigidity, myalgia.

Hypertension

A safety evaluation was carried out in controlled studies in 378 hypertensive patients treated with diltiazem hydrochloride controlled delivery capsules at doses up to 360 mg a day. Adverse effects were reported in 30.7% of patients and required discontinuation of therapy in 2.1%.

The most common adverse effects were headache (8.7%); edema (4.0%); bradycardia (3.7%); dizziness (3.4%), ECG abnormality (2.9%); asthenia (2.6%), and first-degree AV block (2.1%).

The following percentage of adverse effects, divided by system, was reported:

Blood and lymphatic system disorders: Leukopenia (1.1%).

Cardiovascular: Edema peripheral (4.0%), bradycardia (3.7%), ECG abnormalities (2.9%), first degree AV block (2.1%), arrhythmia (1.6%), vasodilation (flushing) (1.6%), bundle branch block (0.8%), cardiomegaly (0.5%), hypotension (0.5%).

Gastrointestinal: Constipation (1.3%), dyspepsia (1.3%), diarrhea (0.6%).

Investigations: ALT increase (0.8%).

Nervous System and psychiatric disorders: Headache (8.7%), dizziness (3.4%), asthenia (2.6%),

somnolence (1.3%), nervousness (1.1%).

Renal and urinary disorders: Nocturia (0.5%).

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: systolic murmur, supraventricular extra systoles, migraine, tachycardia, increased appetite, increase in weight, albuminuria, bilirubinemia, hyperuricemia, thirst, insomnia, vertigo, nausea, pruritus, rash, increased perspiration, polyuria, amblyopia, tinnitus, and elevations in creatine kinase, alkaline phosphatase, and AST.

Overall Diltiazem safety profile

In clinical trials of diltiazem involving over 3300 patients, the most common adverse reactions were headache (4.6%), edema (4.6%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.5%), nausea (1.4%), rash (1.2%), and dyspepsia (1.0%).

The following events were reported with a frequency of less than 1.0%.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extra systoles, congestive heart failure, syncope, palpitations, AV block (second- or third- degree), hypotension, ECG abnormalities.

Dermatological: Petechiae, pruritus, photosensitivity, urticarial.

Eye disorders: Amblyopia, eye irritation.

Gastrointestinal disorders: Anorexia, diarrhea, dysgeusia, dyspepsia, vomiting, weight increase, thirst, constipation.

General disorders and administration site conditions: Malaise (reported as common adverse reaction), osteoarticular pain.

Investigations: Elevations of AST, ALT, LDH, and alkaline phosphatase (see 7 WARNINGS AND PRECAUTIONS), CPK increase.

Metabolism and nutrition disorders: hyperglycemia, hyperuricemia.

Nervous System and psychiatric disorders: Amnesia, depression, gait abnormality, nervousness, somnolence, hallucinations, paresthesia, personality change, tinnitus, tremor, abnormal dreams, insomnia.

Renal and urinary disorders: Nocturia, polyuria.

Respiratory, thoracic, and mediastinal disorders: Dyspnea, epistaxis, nasal congestion.

Sexual dysfunction disturbances and gender identity disorders: Impotence, sexual difficulties.

Vascular disorders: Orthostatic hypotension.

8.5 Post-Market Adverse Reactions

Adverse reactions reported during post marketing experience are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known.

Blood and lymphatic system disorders: Thrombocytopenia, hemolytic anemia, increased bleeding time, leukopenia.

Nervous system and psychiatric disorders: Mood changes including depression, extrapyramidal symptoms.

Cardiac disorders: Sinoatrial block, congestive heart failure, sinus arrest, cardiac arrest (asystole).

Respiratory, thoracic, and mediastinal disorders: Bronchospasm (including asthma aggravation).

Gastrointestinal disorders: Gingival hyperplasia.

Metabolism and nutrition disorders: Hyperglycaemia, diabetes (new onset), worsening of existing diabetes (type 1 or type 2).

Skin and subcutaneous tissue disorders: Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), sweating, exfoliative dermatitis (see 7 WARNINGS AND PRECAUTIONS), acute generalized exanthematous pustulosis, occasionally desquamative erythema with or without fever, allergic reactions, alopecia, purpura.

Vascular disorders: A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis.

Hepatobiliary disorders: Hepatitis.

Renal disorders: Acute kidney injury/failure.

Reproductive system and breast disorders: Gynecomastia.

Eye disorders: Detached retina, retinopathy.

Musculoskeletal and connective tissue disorders: Myopathy.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. 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. However, a definitive cause and effect relationship between these events and diltiazem hydrochloride therapy is yet to be established.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of dantrolene infusion
- Concomitant use of ivabradine
- Concomitant use of lomitapide mesylate
- Concomitant use of Direct Oral Anticoagulants (DOACs; e.g. apixaban, rivaroxaban, dabigatran, see 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

Cytochrome P450 System

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation mainly by the CYP3A4 isoenzyme of the cytochrome P450 system and is a substrate of the P-glycoprotein (P-gp). Diltiazem has also been shown to be an inhibitor of CYP3A4 (moderate) and P-gp.

Co-administration of diltiazem with other drugs which follow the same route of biotransformation or are inhibitors or inducers of these enzymes may result in altered bioavailability of diltiazem or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic index, and especially in patients with renal and/or hepatic impairment, may require adjustment, or discontinuation, when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

9.3 Drug-Behavioural Interactions

Alcohol

Alcohol can exhibit hypotensive effects. Co-administration with antihypertensive agents

including diltiazem may result in additive effects on blood pressure and orthostasis. Patients should be advised that alcohol may potentiate the hypotensive effects of diltiazem, especially during the initiation of therapy and following a dosage increase. Caution should be exercised when rising from a sitting or recumbent position, and patients should notify their physician if they experience dizziness, light-headedness, syncope, orthostasis, or tachycardia.

9.4 Drug-Drug Interactions

DILTIAZEM CD is contraindicated with co-administration of lomitapide mesylate as it may increased concentrations of lomitapide mesylate due to inhibition of CYP3A4 (see 9 DRUG INTERACTIONS).

Co-administration of diltiazem with other drugs which follow the same route of biotransformation or are inhibitors or inducers of these enzymes may result in altered bioavailability of diltiazem or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Table 2 : Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical Comment
Acetylsalicylic acid or antiplatelet drugs such as ticagrelor, cilostazol, clopidogrel, dipyridamole, ticlopidine	T	↑ bleeding	Because of the increased risk of bleeding due to potential or observed additive effect on platelet aggregation combined with vasodilation or prevention of the normal vasoconstrictive response to bleeding, the concomitant administration of acetylsalicylic acid or antiplatelet drugs such as ticagrelor, cilostazol and clopidogrel with diltiazem should be undertaken with caution. Besides, a drug interaction is also plausible with dipyridamole and ticlopidine. Dosage adjustment and safety monitoring may be necessary when coadministration cannot be avoided.
Alpha-antagonists	T	↑ antihypertensive	Concomitant treatment with α-

Proper/Common name	Source of Evidence	Effect	Clinical Comment
			antagonists may produce or aggravate hypotension. The combination of diltiazem with an α-antagonist should be considered only with the strict monitoring of blood pressure.
Amiodarone, digoxin	CT	↑ bradycardia	Severe conduction system abnormalities including heart block of varying degree, sinus arrest and a low cardiac output state of life-threatening severity have been reported following concomitant use of diltiazem and amiodarone. These drugs may also have additive effects on cardiac conduction and contractility. Increased risk of bradycardia is seen with amiodarone. Caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are used.
Anaesthetics	T	↑ depression of cardiac contractility, conductivity, and automaticity	The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.
Benzodiazepines (midazolam, triazolam)	CT	↑ benzodiazepines plasma concentration	Diltiazem significantly increases peak plasma levels and the elimination half-life of triazolam and midazolam. Special care (close medical supervision and/or dose adjustment) should be taken when prescribing short-acting benzodiazepines metabolized by CYP3A4 in patients using diltiazem.

Proper/Common name	Source of Evidence	Effect	Clinical Comment
Beta-Blockers	T, CT	Arrhythmic effect ↑ propranolol exposure	The concomitant administration of diltiazem with beta-adrenergic blocking drugs warrants caution because of rhythm disturbances occurrence, and requires close medical supervision and ECG monitoring, particularly at the beginning of treatment. Such an association may have an additive effect on heart rate, on sino-atrial and AV conduction or on blood pressure (e.g. pronounced bradycardia, sinus arrest, and heart failure) (see 7 WARNINGS AND PRECAUTIONS). Appropriate dosage adjustments may be necessary. A study in five normal subjects showed that diltiazem increased propranolol bioavailability by 50%. An increased risk of depression has been reported when diltiazem is co-administered with beta-blockers (see 8 ADVERSE REACTIONS).
Carbamazepine	CT	↑ Carbamazepine serum level	Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction and dose adjustment of carbamazepine and/or diltiazem may be necessary.
Anti-H_2 agents (Cimetidine, ranitidine)	CT	↑ diltiazem exposure	A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels C_{max} (58%) and area-under-the-curve AUC (53%) after a 1-week course of

Proper/Common name	Source of Evidence	Effect	Clinical Comment
			cimetidine at 1200 mg per day and a single dose of oral diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.
Corticosteroids (methylprednisolone)	T	↑ P-gp plasma concentration	Inhibition of methylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein by diltiazem. Therefore, patients should be monitored when initiating methylprednisolone treatment and a dose adjustment may be necessary.
Cyclosporine	CT	↑ cyclosporine concentration in specific population	Concomitant administration of diltiazem and cyclosporine has resulted in an increase in cyclosporine concentrations. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

Proper/Common name	Source of Evidence	Effect	Clinical Comment
			Downward titration of the cyclosporine dose may be necessary. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.
Dantrolene (infusion)	CT	Ventricular fibrillation effect in animals observed	Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of calcium-channel antagonist and dantrolene is therefore potentially dangerous (see 2 CONTRAINDICATIONS).
Digitalis	CT	↑ digoxin serum level	Diltiazem and digitalis glycosides may have an additive effect in prolonging AV conduction. In clinical trials, concurrent administration of diltiazem and digoxin has resulted in increases in serum digoxin levels with prolongation of AV conduction. This increase may result from a decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should be carefully monitored. The dose of digoxin may need downward adjustment.
Direct Oral Anticoagulants (DOACs; e.g. apixaban, rivaroxaban, dabigatran)	CT	↑DOAC plasma concentration In a pharmacokinetic study, coadministration of apixaban with diltiazem led to a 1.4 and 1.3-fold increase in mean apixaban AUC and C_{max},	Coadministration of diltiazem and DOACs increases the risk of bleeding due to pharmacokinetic interaction via P-gp and CYP3A4. Literature evidence has shown increased risk of bleeding leading to hospitalization and even death in atrial fibrillation patients receiving diltiazem and apixaban, rivaroxaban or dabigatran.

Proper/Common name	Source of Evidence	Effect	Clinical Comment
		respectively.	Concomitant treatment with diltiazem and DOACs in patients should be used with caution. Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially in patients with renal impairment.
Inducers of CYP3A4 (e.g. avasimibe, carbamazepine, phenytoin, rifampin)	T	↓ diltiazem plasma concentration	Diltiazem should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required.
Ivabradine	C	↑ AUC ivabradine (2- 3-fold). Additional heart rate lowering	Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine (see 2 CONTRAINDICATIONS)
Lithium	T	↑ Lithium neurotoxicity	Risk of increased in lithium-induced neurotoxicity.
Lomitapide mesylate	T	↑ AUC lomitapide mesylate (4-10-fold)	Co-administration of lomitapide mesylate with diltiazem is contraindicated (see 2 CONTRAINDICATIONS)
Other antiarrhythmic agents	T	↑ antiarrhythmic effect	Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended (additive risk of increased cardiac adverse effects). This combination should only be used under close clinical and ECG monitoring.
Phenytoin	C	↑ phenytoin plasma concentration	When co-administered with phenytoin, diltiazem may increase phenytoin serum concentration, in some cases, two to three-fold, as reported in spontaneous case reports. Signs and symptoms of

Proper/Common name	Source of Evidence	Effect	Clinical Comment
			phenytoin toxicity include nystagmus, ataxia, dysarthria, tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, and vomiting. Caution should be exercised when diltiazem and phenytoin are co-administered. It is recommended that the phenytoin serum concentration be monitored.
Rifampicin	CT	↓ diltiazem plasma concentration	Administration of diltiazem with rifampicin markedly reduced plasma diltiazem concentrations and the therapeutic effect of diltiazem. Patients should be carefully monitored when initiating or discontinuing rifampicin therapy.
Short and Long-Acting Nitrates	T	↑ vasodilating effect	Increased hypotensive effects and faintness (additive vasodilating effects) are observed when nitrates are co-administered with Calcium Channels Inhibitors. In patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out gradually at increasing doses due to increased hypotensive effects.
Statins (lovastatin, pravastatin)	CT	↑ lovastatin exposure No effect on pravastatin	In a ten-subject study, coadministration of diltiazem with lovastatin resulted in a 3-4 time increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.
Strong inhibitors of CYP3A4 (e.g.,	T	↑ diltiazem plasma concentration	Strong CYP3A4 inhibitors may significantly increase the plasma

Proper/Common name	Source of Evidence	Effect	Clinical Comment
ketoconazole, itraconazole, ritonavir, clarithromycin)			concentrations of diltiazem. Diltiazem should therefore be used with caution together with these agents and monitoring of therapy is required. Appropriate dosage adjustment of diltiazem may be necessary.
Theophylline	T	↑ antihypertensive	Increased antihypertensive effects.
X-Ray Contrast Media	T	↑ hypotension ↑ bradycardia ↑ heart conduction disorder	Cardiovascular effects of an intravenous bolus of an X-ray contrast media, such as hypotension, bradycardia, and heart conduction disorders, may be increased in patients treated with diltiazem. Special caution is required in patients receiving concomitantly diltiazem and X-ray contrast media.

Legend: C=Case Study, CT=Clinical Trial, T=Theoretical

Calcium Antagonists (verapamil, nifedipine)

Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil or to nifedipine, using diltiazem in conjunction with either of these drugs may be beneficial.

9.5 Drug-Food Interactions

Grapefruit Juice

Grapefruit juice may increase the plasma concentrations of orally administered diltiazem in some patients. The proposed mechanism is inhibition of CYP450 3A4-mediated first-pass metabolism in the gut wall by certain compounds present in grapefruit.

Patients who regularly consume grapefruit or grapefruit juice should be monitored for increased adverse effects of diltiazem such as such as headache, irregular heartbeat, edema, unexplained weight gain, and chest pain. Grapefruit and grapefruit juice should be avoided if an interaction is suspected.

Multivitamins with minerals

Calcium-containing products may decrease the effectiveness of calcium channel blockers by saturating calcium channels with calcium. Calcium chloride has been used to manage acute severe verapamil toxicity. Monitoring of the effectiveness of calcium channel blocker therapy is advised during co-administration with calcium products.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the cells through specific ion channels. Diltiazem blocks transmembrane influx of calcium through the slow channel without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Diltiazem does not alter total serum calcium.

Angina

The precise mechanism by which diltiazem relieves angina has not been fully determined but it is believed to be brought about largely by its vasodilator action.

In angina due to coronary spasm, diltiazem increases myocardial oxygen delivery by dilating both large and small coronary arteries and by inhibiting coronary spasm at drug levels which cause little negative inotropic effect. The resultant increases in coronary blood flow are accompanied by dose dependent decreases in systemic blood pressure and decreases in peripheral resistance.

In angina of effort, it appears that the action of diltiazem is related to the reduction of myocardial oxygen demand. This is probably caused by a decrease in blood pressure brought about by the reduction of peripheral resistance and of heart rate.

Hypertension

The antihypertensive effect of diltiazem is believed to be brought about largely by its vasodilatory action on peripheral blood vessels with resultant decrease in peripheral vascular resistance.

10.2 Pharmacodynamics

Diltiazem produces antihypertensive effects both in the supine and standing positions. Resting heart rate is usually slightly reduced. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually unaffected. Heart rate at maximum exercise is reduced.

Studies to date, primarily in patients with normal ventricular function, have shown that cardiac output, ejection fraction and left ventricular end-diastolic pressure have not been affected.

Chronic therapy with diltiazem produces no change, or a decrease, in circulating plasma catecholamines. However, no increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem inhibits the renal and peripheral effects of angiotensin II.

In man intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. Chronic oral administration of diltiazem in doses up to 540 mg per day has resulted in small increases in PR interval. Second degree and third-degree AV block have been observed (see 7 WARNINGS and PRECAUTIONS). In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

10.3 Pharmacokinetics

Diltiazem is considered to be a moderate inhibitor of CYP3A4, increasing the exposure of oral midazolam, a selective substrate of CYP3A4, by 3.8-fold. In an *in vitro* study, diltiazem was both a substrate and inhibitor of the efflux transporter, P-glycoprotein (P-gp). Co-administration of diltiazem with the P-gp probe substrate, digoxin, increased plasma concentrations and exposure of digoxin by approximately 20% and 40%, respectively.

Single oral doses of 30 to 120 mg of diltiazem hydrochloride immediate release tablets result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration. There is a departure from linearity of accumulation of diltiazem when diltiazem tablets are administered to steady-state in normal subjects. A 240 mg daily dose (60 mg QID) gave plasma levels 2.3 times higher than a 120 mg daily dose (30 mg QID) and a 360 mg daily dose (90 mg QID) had levels 1.7 times higher than the 240 mg daily dose.

More than 95% of drug is absorbed from the diltiazem hydrochloride controlled delivery

capsules formulation. A single 360 mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours. When diltiazem hydrochloride controlled delivery capsules was taken with a high fat content breakfast, the extent of diltiazem absorption was not affected but was delayed. Dose-dumping does not occur.

A departure from linearity similar to that seen with diltiazem hydrochloride tablets is observed. As the dose of diltiazem hydrochloride controlled delivery capsules is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area under the curve (AUC) of 2.7 times. When the dose is increased from 240 mg to 360 mg there is an increase in AUC of 1.6 times.

A study which compared patients with normal hepatic function to liver cirrhosis patients noted an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single dose study in patients with severely impaired renal function showed no difference in the half-life of diltiazem as compared to patients with normal renal function (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Absorption

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 about 40%.

Distribution

Therapeutic blood levels appear to be in the 50 to 200 ng/mL range and the plasma elimination half-life (beta-phase) following single or multiple drug administration is approximately 3.5 to 6.0 hours. In vitro human serum binding studies revealed that 70 to 80% of diltiazem is bound to plasma proteins.

Metabolism

The metabolic pathways of diltiazem include N- and O-demethylation (via cytochrome P-450), deacetylation (via plasma and tissue esterases), in addition to conjugation (via sulfation and glucuronidation). *In vitro* studies have demonstrated that CYP 3A4 is the principal CYP isoenzyme involved in N- demethylation. The major metabolite, desacetyl diltiazem, is present in the plasma at levels 10 to 20% of the parent drug and is 25 to 50% as potent as diltiazem in terms of coronary vasodilation.

Elimination

Diltiazem undergoes extensive hepatic metabolism in which only 2 to 4% of the drug appears unchanged in the urine and 6 to 7% appears as metabolites. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C.

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

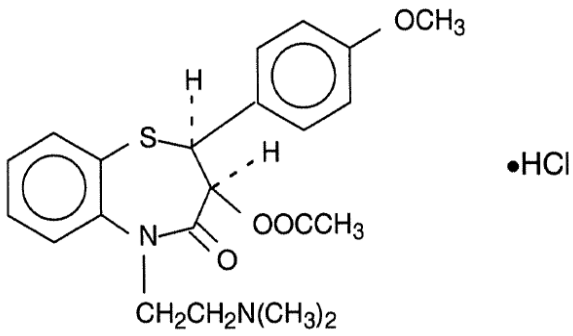
Drug Substance

Proper name: Diltiazem Hydrochloride

Chemical name: Chemically, diltiazem hydrochloride is 1 ,5-benzothiazepin-4(5H)-one,3-(acetyloxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis

Molecular formula and molecular mass: $C_{22}H_{26}N_2O_4S.HCl$, 450.98 g/mol

Structural formula:



Physicochemical properties:

Description: The compound is a white crystalline substance or powder having a bitter taste or odour.

Solubility: Diltiazem is considered freely soluble in water, methanol, or chloroform, slightly soluble in absolute ethanol and barely soluble in benzene.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of DILTIAZEM CD 300 mg controlled-delivery capsules (Sivem Pharmaceuticals ULC) with CARDIZEM® CD 300 mg controlled-delivery capsules (Nordic Laboratories Inc.) was conducted in healthy, adult,

male subjects under fed conditions. Comparative bioavailability data from the 15 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 300 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	2424.5 2787.0 (59.0)	2515.6 3000.8 (65.3)	96.4	83.6 – 111.1
AUC_I (ng·h/mL)	2485.2 2856.1 (59.2)	2599.7 3097.5 (65.4)	95.6	83.2 – 109.8
C_{max} (ng/mL)	134.9 155.0 (52.9)	121.7 141.3 (58.4)	110.8	93.6 – 131.3
T_{max}[3] (h)	8.4 (48.6)	16.0 (49.6)		
$T_{1/2}$[3] (h)	4.8 (28.3)	5.2 (28.4)		

[1] DILTIAZEM CD (diltiazem hydrochloride) controlled-delivery capsules, 300 mg (Sivem Pharmaceuticals ULC)

[2] CARDIZEM® CD (diltiazem hydrochloride) controlled-delivery capsules, 300 mg (Nordic Laboratories Inc.)

[3] Expressed as the arithmetic mean (CV %) only

A randomized, two-way, single-dose, crossover comparative bioavailability study of DILTIAZEM CD 300 mg controlled-delivery capsules (Sivem Pharmaceuticals ULC) with CARDIZEM® CD 300 mg controlled-delivery capsules (Nordic Laboratories Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 16 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 300 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	2036.5 2133.0 (29.6)	2027.1 2192.3 (38.1)	100.5	87.9 – 114.8
AUC_I (ng·h/mL)	2065.7 2158.5 (29.1)	2044.0 2226.0 (38.5)	101.1	88.1 – 116.0
C_{max} (ng/mL)	107.1 111.6 (28.9)	117.9 127.3 (38.8)	90.8	80.3 – 102.7
T_{max}[3] (h)	10.6 (57.2)	11.2 (51.7)		
$T_{1/2}$[3] (h)	5.6 (21.1)	6.0 (21.9)		

[1] DILTIAZEM CD (diltiazem hydrochloride) controlled-delivery capsules, 300 mg (Sivem Pharmaceuticals ULC)

[2] CARDIZEM® CD (diltiazem hydrochloride) controlled-delivery capsules, 300 mg (Nordic Laboratories Inc.)

[3] Expressed as the arithmetic mean (CV %) only

A randomized, two-way, multiple-dose, crossover comparative bioavailability study of DILTIAZEM CD 300 mg controlled-delivery capsules (Sivem Pharmaceuticals ULC) with CARDIZEM® CD 300 mg controlled-delivery capsules (Nordic Laboratories Inc.), administered as 1 x 300 mg controlled-delivery capsules once a day for seven days, was conducted in healthy, adult, male subjects. Comparative bioavailability data from the 16 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 300 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{tau,ss}$ (ng·h/mL)	3121.8 3345.0 (37.5)	3100.0 3307.1 (35.7)	100.7	91.9 – 110.3
$C_{max,ss}$ (ng/mL)	205.9 220.1 (37.8)	200.4 213.9 (36.0)	102.7	92.8 – 113.8
$C_{min,ss}$ (ng/mL)	73.8 82.7 (46.8)	80.4 89.4 (45.6)	91.7	80.4 – 104.5
T_{max}[3] (h)	7.3 (40.1)	7.0 (64.9)		
FL[3] (%)	101.5 (25.1)	93.9 (35.5)		

[1] DILTIAZEM CD (diltiazem hydrochloride) controlled-delivery capsules, 300 mg (Sivem Pharmaceuticals ULC)

[2] CARDIZEM® CD (diltiazem hydrochloride) controlled-delivery capsules, 300 mg (Nordic Laboratories Inc.)

[3] Expressed as the arithmetic mean (CV %) only

A randomized, two-way, multiple-dose, crossover comparative bioavailability study of DILTIAZEM CD 120 mg controlled-delivery capsules (Sivem Pharmaceuticals ULC) with CARDIZEM® CD 120 mg controlled-delivery capsules [Marion Merrell Dow (Canada) Inc.], administered as 1 x 120 mg controlled-delivery capsules once a day for seven days, was conducted in healthy, adult, male subjects. Comparative bioavailability data from the 16 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 120 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{tau,ss}$ (ng·h/mL)	775.3 827.1 (33.9)	779.2 825.2 (32.8)	99.5	87.5 – 113.1
$C_{max,ss}$ (ng/mL)	55.0 58.3 (33.2)	55.8 58.4 (30.7)	98.6	85.4 – 113.8
$C_{min,ss}$ (ng/mL)	16.7 17.2 (49.5)	15.3 16.7 (42.5)	104.3	85.2 – 127.8
T_{max}[3] (h)	7.9 (42.3)	8.0 (61.9)		
FL[3] (%)	124.2 (17.1)	125.2 (21.1)		

[1] DILTIAZEM CD (diltiazem hydrochloride) controlled-delivery capsules, 120 mg (Sivem Pharmaceuticals ULC)

[2] CARDIZEM® CD (diltiazem hydrochloride) controlled-delivery capsules, 120 mg [Marion Merrell Dow (Canada) Inc.]

[3] Expressed as the arithmetic mean (CV %) only

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Table 3: Acute Toxicity

Route	Animal	Sex	LD_{50} (mg/kg)	LD_{50} 95% Confidence Limits (mg/kg)
Oral	mice	M&F	415 - 700	(343 - 736)
	rats	M&F	560 - 810	(505 - 1004)
s.c.	mice	M&F	260 - 550	(220 - 672)
i.p.	mice	M&F	187	(165 - 211)
	rats	M&F	211	(155 - 287)
i.v.	mice	M&F	58 - 61	(52 - 69)
	rats	M&F	38 - 39	(34 - 44)

Toxic effects appeared rapidly, and toxicity included reduction of spontaneous activity, ptosis, piloerection, ataxia, loss of muscle tone, and loss of righting reflex. Gross autopsy of animals that died as well as the survivors revealed no abnormalities.

Tolerance was evaluated in rabbits and dogs. Dogs received oral doses of 12.5, 25, 50 or 100 mg/kg. Ataxia, disorientation, decreased activity, diuresis, and mydriasis were noted at 25 mg/kg. In addition, heavy sedation and emesis were seen at 50 mg/kg. At 100 mg/kg, convulsions occurred, and one of the two animals died. Rabbits received 100, 200, 300, 400 mg/kg. The major symptoms were decreased activity, increased respiration, salivation and opisthotonos. One of the two rabbits died at 300 mg/kg and the two rabbits in the 400 mg/kg group died.

Subacute Toxicity

In rats, oral doses of 10, 20, 50, 100, 250 or 500 mg/kg/day of diltiazem were administered for 28 or 30 days. The relative liver weights of animals receiving 250 mg/kg/day, and 500 mg/kg/day were increased. Microscopic examination revealed drug related degeneration of hepatic and renal cells in the highest dose group.

When the drug was given to rats intraperitoneally at 25 mg/kg/day for 30 days, hepatic and renal cell degeneration was seen. Macular hyaloid degeneration of the heart also was seen in 50% of the rats in this study.

Thirty-day subacute studies in dogs revealed hepatic and renal cell degeneration when diltiazem was given at doses of 25 mg/kg/day orally and 5 mg/kg/day intravenously. Two dogs out of 5 receiving 50 mg/kg/day orally, died.

Carcinogenicity

In mice, diltiazem was administered at doses of 5, 15 or 30 mg/kg/day for a period of 21 months in females. Because of a lower survival, males were terminated at 20 months. Gross and histopathological examination failed to reveal any treatment related increase in the incidence of either neoplastic or other toxic lesions.

Rats received 6.25, 25 or 100 mg/kg/day of diltiazem for 24 months. An additional group received 200 mg/kg for 12 months. Treatment was terminated at 23 months in females receiving 100 mg/kg because of the low survival. Females had increased weight gain at 100 and 200 mg/kg, food consumption was increased among both sexes at these dose levels. Organ weight data revealed a significant increase in liver weight for rats of both sexes given 200 mg/kg. Microscopic evaluation revealed some evidence of dose dependent hepatic cytoplasmic vacuolization in rats treated with doses of 100 and 200 mg/kg/day and killed at 12 months. At 24 months, there were similar findings in control and treated animals. There was no increase in the incidence of neoplastic or other toxic lesions in rats treated with diltiazem.

Diltiazem was administered orally to dogs for 12 months at doses of 5, 10, 20 mg/kg/day. A dose related suppression of body weight gain became noticeable after 6 months.

Mutagenicity

No mutagenic changes were observed in the recombination test and two Ames reverse mutagenicity assays.

Reproductive and Developmental Toxicology

Table 4: Results in mice

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring
oral	10, 25, 50, 100, 200, 400	Day 7 to day 12	High incidence of vertebral column malformations when more than 50 mg/kg was administered.
oral	Single doses of 12.5, 25, 50, 100, 200	One of days 7 to 14	Cleft palate and malformation of extremities or trunk were significantly higher when 50 or 100 mg/kg was administered on day 12. Vertebral malformations were most prevalent when 50 or 100 mg/kg was administered on day 9.
intra-peritoneal	0.2, 3.1, 6.3, 12.5, 25	Day 7 to day 12	Fetal mortality greatly increased when 12.5 mg/kg or more was administered. No teratogenic effect was demonstrated.
intra-peritoneal	Single doses of 3.1, 6.3, 12.5, 25, 50	One of days 5 to 16	Brachydactyly and hematoma in the extremities when 50 mg/kg was administered on day 13. Vertebral column malformations from the thoracic to coccygeal level and malformations of the ribs were observed when a dose of 25 mg/kg or greater was administered on day 9.
oral	10, 50, 100, 200, 400	Day 9 to 14	No teratogenic effect. High fetal death rate when 200 & 400 mg/kg was administered.
oral	10, 30, 100	Day 6 to 15	No teratogenic effect.
oral	Single doses of	On one of days 9	Significant incidence of skeletal

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring
	300, 400, 600	to 14	malformations involving vertebrae & sternebrae when 400 mg/kg was administered on day 11. General edema, short or absent tail was observed when 600 mg/kg was administered on day 12.
intra-peritoneal	0.2, 2.0, 20, 40, 80	Day 9 to 14	Brachydactyly & hematoma in the front paw and tail and a high fetal mortality rate were observed when 80 mg/kg was administered.
intra-peritoneal	80	Day 9 to 11	Vertebral anomalies.
intra-peritoneal	80	Day 12 to 14	Brachydactyly, hematoma of the front paw and tail deformities and high fetal mortality rate.
intra-peritoneal	Single dose of 80	One of days 9 to 14	Fetal mortality increased on day 11 reached 100% on day 12 and decreased thereafter. Limb and tail deformities were induced when 80 mg/kg was administered on day 13 & 14. Vertebral column deformities were induced when 80 mg/kg was administered on day 11.
	Single doses of 40	One of days 11 to 14	No teratogenic effect.
oral	17.5, 35, 70	Day 6 to 18	Significant increase in skeletal malformations occurred when 35 mg/kg was administered. All pregnant dams aborted between days 21 and 25 of gestation when 70 mg/kg was administered.
intra-peritoneal	6.3, 12.5, 25	Day 7 to 16	Fetal mortality greatly increased at 12.5 mg/kg and reached 100% at 25 mg/kg. Skeletal defects and external malformations were induced when 12.5 mg/kg was administered. Their incidence was not statistically significant due to the low number of surviving fetuses.

In fertility studies female rats received doses of 12.5, 25, 50 and 100 mg/kg p.o. In the 100 mg/kg group there was a reduction in the number showing a positive mating. However, the

overall pregnancy rates and the average pre-coital time were comparable.

In peri- and post-natal studies, rats received diltiazem in doses of 10, 30 or 100 mg/kg/day from day 14 of gestation through day 21 postpartum. Diltiazem was associated with a reduction in early individual weights and survival rates of the pups. At 100 mg/kg/day dystocia was evident. Retinal and tongue malformations were more frequent in the offspring of the 30 and 100 mg/kg/day group.

***In Vitro* Observations**

Initial experimental work revealed that diltiazem was a coronary and peripheral vasodilator. Subsequent work substantiated that diltiazem's smooth muscle relaxant effect, as well as negative inotropic effect, resulted from the drug's ability to block excitation-contraction coupling by inhibiting slow calcium channel conduction. In a muscle bath study with isolated human coronary artery segments obtained at the time of cardiac transplantation, diltiazem produced nearly complete relaxation of potassium-contracted segments.

Studies in various experimental models have confirmed the negative inotropic effect of diltiazem.

At low doses (1.1×10^{-7} M) diltiazem caused a reduction in contractile force of guinea pig papillary muscle with no demonstrable effect on the action potential. However, at higher concentrations (1.1×10^{-5} M) both a decrease in contractile tension and a lowering of maximum dp/dt were seen.

Studies done in isolated perfused rat hearts showed that diltiazem (10^{-6}M) decreases contractility without affecting action potential duration or resting membrane potential. In several experimental models it has been shown that the concentration of diltiazem required to produce smooth muscle relaxation and vasodilation is significantly less than the concentration required to produce a negative inotropic effect.

***In Vivo* Observations**

Pharmacodynamics

Experiments in both open and closed chest dog models indicate that diltiazem increases coronary blood flow and reduces coronary vascular resistance. Intravenous diltiazem (100 mcg/kg) increased coronary blood flow by 90%, with a predominant effect on large coronary arteries and collaterals. Increase in coronary blood flow has also been shown following diltiazem administration in both the epicardial and subendocardial regions in ischemic and non-ischemic models. There was also a dose-related decrease in mean aortic pressure and systemic vascular resistance with an increase in stroke volume and cardiac output. No significant change was noted in determinants of LV function such as LVEDP or LV dP/dT. The reduction in blood pressure that is seen with diltiazem is due to a direct vasodilatory effect on the blood vessels

and is not mediated by sympathetic alpha receptor blockade, beta receptor stimulation, or ganglionic blockade. Diltiazem has been shown to inhibit the pressor responses induced by norepinephrine and angiotensin II.

In animal studies, the negative inotropic effect of diltiazem appears to be offset by its ability to decrease afterload and induce a mild reflex adrenergic response.

Pharmacokinetics

The effect of diltiazem on the pharmacokinetics of phenytoin was investigated in rats. Animals were given 20 mg/kg i.p. phenytoin alone or phenytoin together with 5 mg/kg i.p. diltiazem and the plasma samples were collected at different time intervals. The study showed that diltiazem significantly ($p<0.05$) increased phenytoin AUC (4-fold), C_{max} (2-fold), and elimination half-life ($t_{½}$ from 1.1h to 2.0h), in the rat.

17 SUPPORTING PRODUCT MONOGRAPHS

1. CARDIZEM® CD (Diltiazem Hydrochloride Controlled Delivery Capsules, 120 mg, 180 mg, 240 mg and 300 mg), submission control 291522, Product Monograph, Bausch Health, Canada Inc. (MAR 25, 2025).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] DILTIAZEM CD

Diltiazem Hydrochloride Controlled Delivery Capsules

This patient medication information is written for the person who will be taking **DILTIAZEM CD**. This maybe you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **DILTIAZEM CD**, talk to a healthcare professional.

What DILTIAZEM CD is used for:

DILTIAZEM CD is used in adults to:

- control chest pain that most often occurs with physical activity or emotional stress (chronic stable angina). It can be used with other chest pain medicines when those medicines do not provide enough benefit on their own. DILTIAZEM CD is normally used in patients who have tried other treatments for their chest pain, but did not receive benefits, or had bad side effects.
- treat mild to moderate high blood pressure.

How DILTIAZEM CD works:

DILTIAZEM CD belongs to a group of medicines called “calcium channel blockers” or “calcium antagonists”. It works by:

- relaxing the arteries, which allows blood to flow freely through them. This helps to lower blood pressure.
- reducing the amount of oxygen that your heart muscle needs. This helps to control chest pain.

The ingredients in DILTIAZEM CD are:

Medicinal ingredients: Diltiazem Hydrochloride.

Non-medicinal ingredients: Eudragit, FD&C blue #1, gelatin, iron oxide black (300 mg only) methacrylic acid copolymer, methylcellulose, microcrystalline cellulose, polysorbate 80, talc, titanium dioxide and tributyl citrate.

DILTIAZEM CD comes in the following dosage forms:

- Controlled-delivery capsules: 120 mg, 180 mg, 240 mg, and 300 mg.

Do not use DILTIAZEM CD if:

- you are allergic to diltiazem or any other ingredients in DILTIAZEM CD or its container.
- you have any heart rhythm disorders and do not have a pacemaker.
- you have very low blood pressure (less than 90 mmHg systolic).
- you have a very slow heartbeat (less than 40 beats/minute).
- you have had a heart attack and have fluid in your lungs as a result of heart failure.
- you are pregnant or plan to become pregnant.
- you are a woman of child-bearing potential, unless you and your healthcare professional have decided you should take DILTIAZEM CD.
- you are breastfeeding or planning to breastfeed.
- you are taking the following medicines:
  - dantrolene, used to treat severe muscle spasms or severe fever.
  - ivabradine, used to treat heart failure.
  - lomitapide mesylate, used to treat high blood cholesterol.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive DILTIAZEM CD. Talk about any health conditions or problems you may have, including if you:

- have heart, liver or kidney disease.
- had a recent heart attack.
- have a history of heart failure.
- are at risk of developing an intestinal obstruction (blockage).
- have asthma or other breathing problems. DILTIAZEM CD may cause your symptoms to get worse, especially after a dose increase.
- have high blood sugar or diabetes.
- are 65 years of age or older.

Other warnings you should know about:

DILTIAZEM CD can cause serious side effects, including:

- **Kidney problems:** DILTIAZEM CD can cause kidney problems, even at prescribed doses. You are at higher risk if you have heart failure, a very slow heartbeat or very low blood pressure.
- **Hyperglycemia (high blood sugar):** DILTIAZEM CD may affect your blood sugar. If you have diabetes, closely monitor your blood sugar while taking DILTIAZEM CD and report

any unusual results to your healthcare professional.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Surgery: Tell any doctor, dentist, pharmacist, or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have surgery (including dental procedures).

Pregnancy:

- Avoid becoming pregnant while you are taking DILTIAZEM CD. If you are able to get pregnant, you should use effective birth control (contraception) during your treatment. Talk to your healthcare professional about the best kind of birth control to use while you are taking DILTIAZEM CD.
- If you take DILTIAZEM CD during pregnancy, it may harm your unborn baby. Your healthcare professional will discuss the risks with you.
- If you discover that you are pregnant, stop taking DILTIAZEM CD and tell your healthcare professional right away.

Breastfeeding: DILTIAZEM CD passes into breast milk and may harm your baby. Do not breastfeed during treatment with DILTIAZEM CD. Talk to your healthcare professional about ways to feed your baby during this time.

Adults (65 years of age or older): Side effects like swelling of the arms or legs, irregular heartbeat, dizziness, skin rash and frequent urination may happen more often. Your healthcare professional might adjust your dose of DILTIAZEM CD. They will monitor your health during and after treatment.

Checks-up and testing:

- You will have regular visits with your healthcare professional while you are taking DILTIAZEM CD to monitor your health. They will:
    - do blood and urine tests to check your liver and kidney health, and the level of sugar in your blood.
    - check your lungs and verify if you have any breathing problems.
- DILTIAZEM CD can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

Serious Drug Interactions

Do not take DILTIAZEM CD with:

- dantrolene, used to treat severe muscle spasms or severe fever.
- ivabradine, used to treat heart failure.
- lomitapide mesylate, used to treat high blood cholesterol.

Serious drug interactions with DILTIAZEM CD include:

- medicines used to prevent and treat blood clots (Direct Oral Anticoagulants (DOACs)) such as dabigatran, rivaroxaban, apixaban.

Taking DILTIAZEM CD with any of these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure, you are taking these medicines.

The following may also interact with DILTIAZEM CD:

- medicines used to treat fungal infections with a name ending in “azole”.
- medicines used to treat bacterial infections, such as rifampin, erythromycin, clarithromycin.
- medicines used to treat high blood pressure, such as alpha antagonists, beta blockers.
- heart medications, such as amiodarone, digoxin, digitalis, flecainide, nifedipine, propafenone, quinidine, verapamil.
- medicines used to treat chest pain (angina), such as short or long-acting nitrates.
- medicines used to control seizures, such as carbamazepine, phenytoin, phenobarbital.
- medicines used to lower blood cholesterol, such as “statins”.
- medicines used to reduce stomach acid and treat ulcers in the stomach or intestines, such as cimetidine, ranitidine.
- medicines used to treat inflammation, such as corticosteroids (including methylprednisolone).
- acetylsalicylic acid (ASA, or ASPIRIN) or medicines used to prevent blood clots, such as ticagrelor, cilostazol, clopidogrel, dipyridamole, ticlopidine, warfarin.
- sleeping pills, such as benzodiazepines (midazolam, triazolam).
- anesthetics.
- cyclosporine, used to control the immune system.
- lithium, used to treat bipolar disorder.
- imipramine, used to treat depression.
- theophylline, used to treat asthma or other lung diseases.
- terfenadine, used to treat allergies.
- ritonavir, used to treat HIV/AIDS.
- products that contain calcium such as multivitamins with minerals.

- X-ray contrast agents.

Alcohol

Drinking alcohol while taking DILTIAZEM CD may cause low blood pressure and dizziness when you go from lying or sitting to standing up. This is more likely to occur after the first dose or when the dose is increased. Tell your healthcare professional if you experience dizziness, light-headedness, fainting, decreased blood pressure or increased heart rate.

Grapefruit juice

Drinking grapefruit juice while taking DILTIAZEM CD may cause headache, irregular heartbeat, edema (swelling), unexplained weight gain, and chest pain. Tell your healthcare professional if this happens to you. Your healthcare professional may recommend that you avoid grapefruit juice while taking DILTIAZEM CD.

How to take DILTIAZEM CD:

- Your dose is tailored/personalized just for you. Take DILTIAZEM CD exactly as your healthcare professional tells you.
- DILTIAZEM CD is taken once a day.
- Swallow capsules whole. Do not chew or crush capsules.
- Do not increase or decrease your dose without consulting your healthcare professional. Taking higher doses can lead to more side effects and a greater chance of overdose.

Usual dose:

To control chest pain:

- **Usual starting dose:** 120 mg to 180 mg once a day.
- Your dose may be slowly (over 7 to 14 days) increased up to 360 mg once a day. Follow your healthcare professional's instructions carefully.

To treat high blood pressure:

- **Usual starting dose:** 180 mg to 240 mg once a day. 120 mg a day may be used in some patients.
- **Maximum dose:** 360 mg a day.

Overdose:

Signs of an overdose with DILTIAZEM CD include:

- very slow or irregular heartbeat.
- very low blood pressure.
- kidney problems.
- heart does not pump blood as well as it should or suddenly stops beating.

If you think you, or a person you are caring for, have taken too much DILTIAZEM CD, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your next dose as scheduled. Do not take two doses at once to make-up for a missed dose.

Possible side effects from using DILTIAZEM CD:

These are not all the possible side effects you may have when taking DILTIAZEM CD. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Headache, dizziness, malaise.
- Nausea (feeling like vomiting).
- Flushing (facial redness) or feeling unusually warm.
- Unusual tiredness and weakness.
- Upset stomach or indigestion.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Fast, slow, or irregular heartbeat		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up).	√		
Peripheral edema (swelling of the legs or hands): swollen or puffy legs, ankles, or hands, feeling heavy, achy, or stiff	√		
Respiratory tract infection (a cold): runny or stuffy nose, sore throat, cough, sinus congestion, body aches, headache, sneezing, fever, generally feeling unwell		√	
UNCOMMON			
Angina (chest pain): discomfort in the shoulder, arm, back, throat, jaw, or teeth; pain or pressure in the chest		√	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse	√		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Eye problems: blurred vision, loss of vision in the eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids	√		
Heart block (a disease in the electrical system of the heart): light-headedness, fainting, irregular heartbeat			√
Heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, leg swelling in legs, ankles and feet, cough, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		√	
Hyperglycemia (high blood sugar): increased thirst and hunger, frequent urination, thirst, and hunger headache, blurred vision, fatigue	√		
RARE			
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
test results, mental status changes (drowsiness, confusion, coma)			
Liver problems: yellowing of the skin or eyes, dark urine, stomach pain or swelling, nausea, vomiting, unusual tiredness		√	
Severe skin reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about DILTIAZEM CD:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sivem.ca, or by calling 1-855-788-3153.

This leaflet was prepared by Sivem Pharmaceuticals ULC.

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