PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ACT DILTIAZEM T

Diltiazem Hydrochloride,
Extended-Release Capsules, 120 mg, 180 mg, 240 mg, 300 mg and 360 mg, oral

Manufacturer's Standard

Antihypertensive Agent
Antianginal Agent

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

Date of Initial Authorization:
August 07, 2014

Date of Revision:
September 08 , 2023

Submission Control Number: 275486

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	09/2023

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACT Diltiazem T (Diltiazem Hydrochloride Extended-Release Capsules) is indicated for:

- **Essential Hypertension**
  ACT Diltiazem T is indicated for the treatment of mild to moderate essential hypertension.

  Safety of concurrent use of diltiazem hydrochloride extended release capsule with other antihypertensive agents has not been established.

- **Chronic Stable Angina**
  ACT Diltiazem T 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 these agents.(See 7 WARNINGS AND PRECAUTIONS, Use with Beta-Blockers)

  ACT Diltiazem T 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, Use with Beta-Blockers).

  Since the safety and efficacy of diltiazem hydrochloride extended release capsule in the management of unstable or vasospastic angina has not been substantiated, its use for these indications is not recommended

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use

1.2 Geriatrics

Geriatrics (> 65 years old): Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires particular care in titration (See 7.1.4 WARNINGS AND PRECAUTIONS, Geriatrics and 9.4 Drug-Drug Interactions).

2 CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated:

- In patients with sick sinus syndrome except in the presence of 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 severe 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 child-bearing potential (See 7.1.1 Pregnant Women);
- During breast-feeding;
- With concomitant use of dantrolene infusion (See 9.4 Drug-Drug Interactions);
- With concomitant use of ivabradine (See 9.4 Drug-Drug Interactions);
- 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

Diltiazem hydrochloride extended-release capsules has not been shown to be bioequivalent to other diltiazem formulations (See 10.3 Pharmacokinetics).

4.2 Recommended Dose and Dosage Adjustment

Hypertension

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.

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

The dosage of ACT Diltiazem T or concomitant antihypertensive agents may need to be adjusted when adding one to the other. (See 7 WARNINGS and PRECAUTIONS, Use with Beta-Blockers).

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.

There is limited experience with doses above 360 mg. However, the incidence of adverse events 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.

4.4 Administration

ACT Diltiazem T should not be chewed or crushed

4.5 Missed Dose

If you miss a dose, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and take your next dose as scheduled. Do not take two doses at the same time.

5 OVERDOSAGE

There have been reports of diltiazem overdose in doses ranging from less than 1g 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. 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 utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and intravenous calcium.

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 10-20 minutes as necessary. Calcium gluconate has also been administered 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. The following measures may be considered:

Bradycardia

Administer atropine. If there is no response to vagal blockage, 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

Vasopressors (e.g. dopamine or levarterenol bitartrate). Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules: 120 mg, 180 mg, 240 mg, 300 mg and 360 mg.	Ethylcellulose, Gelatin, Hydroxypropyl Methylcellulose, Magnesium Stearate, Polymethacrylate, Polysorbate, Povidone, Sugar Spheres, Talc and Titanium Dioxide. Dyes: D&C red #28 (120mg, 240 mg, 300 mg); FD&C blue #1(120mg ,240 mg, 300mg); Black iron oxide (180mg, 300

		mg); FD&C green #3(180mg240 mg 360 mg).

ACT Diltiazem T Extended-Release Capsules are available in the following strengths:

120 mg: Each gelatin capsule, purple opaque cap and body, imprinted RXP 120 in white on the body, containing off-white round pellets.

180 mg: Each gelatin capsule, green opaque cap and white opaque body, imprinted RXP 180 in black on the body, containing off-white round pellets .

240 mg: Each gelatin capsule, purple opaque cap and green opaque body, imprinted RXP 240 in white on the body, containing off-white round pellets.

300 mg: Each gelatin capsule, purple opaque cap and white opaque body, imprinted RXP 300 in black on the body, containing off-white round pellets.

360 mg: Each gelatin capsule, green opaque cap and body, imprinted RXP 360 in white on the body, containing off-white round pellets.

Bottles of 100.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac Conduction

Diltiazem hydrochloride 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 (13 of 3007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.

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 also 2 CONTRAINDICATIONS). 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.

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.

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, cardiac 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 with no overall effect on mortality. Although there has not been a study of sustained release formulation of diltiazem in acute myocardial infarction, 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, AST, ALT 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.

Because diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidney and in bile, monitoring of laboratory parameters and cautious dosage titration are recommended in patients with impaired hepatic or renal function (see 8 ADVERSE REACTIONS).

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

Fetal malformations and adverse effects on pregnancy have been reported in animals. In repeated dose studies a high incidence of vertebral column malformations were present in the offspring of mice receiving more than 50 mg/kg of diltiazem hydrochloride orally.

7.1.2 Breast-feeding

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of ACT Diltiazem T is deemed essential, an alternative method of infant feeding should be instituted.

7.1.3 Pediatrics

Safety and effectiveness in children have not been established.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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%).

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 in identifying and approximating rates of adverse drug reactions in real-world use.

Angina
The safety of diltiazem hydrochloride extended-release capsule was evaluated in 158 patients with chronic stable angina pectoris treated with diltiazem hydrochloride extended-release capsule at doses from 120 to 360 mg per day and in 50 patients treated with placebo. Thirty three percent of the diltiazem hydrochloride extended-release capsule treated patients had one or more adverse events compared to 18% in the placebo group. Discontinuation due to adverse events was required in 3 patients who were on diltiazem hydrochloride extended-release capsule 240 mg/day. The most common adverse events were: headache (8%), pain (4%), dizziness (3%) and peripheral edema (2%).

The following percentages of adverse effects, divided by system, were reported:

- ***Cardiovascular*:** Edema, peripheral (1.8%), palpitations (1.2%), arrhythmia (1.2%).
- ***Central Nervous System:*** Headache (8.2%), asthenia (0.6%), dizziness (3.1%).
- ***Gastrointestinal:*** Constipation (1.2%), dyspepsia (1.2%).

- ***Other:*** Pain (3.7%), pharyngitis (1.8%), cough increase (1.2%), gout (1.2%), rash (1.2%), hyperglycemia (1.2%), albuminuria (1.2%), crystalluria (1.2%), dyspnea (0.6%), infection (0.6%).

Hypertension
A safety evaluation was carried out in placebo-controlled studies in which 345 hypertensive patients (diltiazem hydrochloride extended-release capsules n=243; placebo n=102) were treated with diltiazem hydrochloride extended-release capsules at doses up to 360 mg per day. The most common adverse effects were: headache (13%); edema (5%); GI disease (5%); pain (4%); vasodilation (3%); asthenia (3%); dizziness (3%); and palpitations (2%).

The following percentages of adverse effects, divided by system, were reported:

- ***Cardiovascular:*** Edema, including peripheral edema (5%), vasodilation, including hypotension, syncope and flushing (3%), palpitations (2%), and tachycardia (1%).

- ***Central Nervous System:*** Headache (13%), asthenia (3%), dizziness (3%), neck rigidity (1%), nervousness (1%), paresthesia (1%).

- ***Gastrointestinal:*** GI disease, including dyspepsia, nausea (5%), constipation (1%), anorexia (1%), dry mouth (1%).

- ***Other:*** Pain (4%), pharyngitis (2%), rhinitis (1%), dyspnea (1%), allergic reaction (1%), polyuria (1%), rash (1%).

The most common adverse effects for placebo treated patients in the above mentioned trials were: headache (17%), asthenia (6%), pain (5%), dizziness (4%), edema (3%), GI disease (2%), palpitations (2%), pharyngitis (2%), rhinitis (2%), nervousness (2%), paresthesia (2%), tachycardia (2%), vasodilation (1%), dyspnea (1%).

8.3 Less Common Clinical Trial Adverse Reactions

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

- ***Cardiac disorders:*** Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

- ***Dermatological:*** Petechiae, photosensitivity, pruritus, urticaria.

- ***Eye Disorders:*** Amblyopia, eye irritation.

- ***Gastrointestinal disorders:*** Anorexia, constipation, diarrhea, dry mouth, dysgeusia, thirst, vomiting, weight increase.

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

- ***Investigations:*** Mild elevations of AST, ALT, LDH, and alkaline phosphatase (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Use with Beta-Blockers).

- ***Metabolism and Nutrition Disorders:*** Hyperglycaemia, hyperuricemia.

- ***Nervous System and Psychiatric Disorders:*** Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality change, somnolence, tinnitus, tremor.

- ***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 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

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, lightheadedness, syncope, orthostasis, or tachycardia.

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

9.4 Drug-Drug Interactions

Table 2- Established or Potential Drug-Drug Interactions

Agent	Source on Evidence	Effect	Clinical comment
Acetylsalicylic acid or other antiplatelet drugs (e.g., cilostazole, ticagrelor)	T	↑ bleeding	Because of the increased risk of bleeding due to potential additive effect on platelet aggregation, the concomitant administration of acetylsalicylates or antiplatelet drugs with diltiazem should be undertaken with caution.
Alpha-antagonists	T	↑ antihypertensive	Concomitant treatment with α-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	T	↑ bradycardia	Caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are

Agent	Source on Evidence	Effect	Clinical comment
			used.
Anesthetics	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 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.
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 a synergetic 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%.
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

Agent	Source on Evidence	Effect	Clinical comment
			carbamazepine and/or diltiazem may be necessary.
Anti-H2 agents (cimetidine, ranitidine)	CT	↑ cimetidine, ranitidine 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 cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P450, the enzyme system responsible for the first-pass metabolism of diltiazem. 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	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

Agent	Source on Evidence	Effect	Clinical comment
			discontinued. 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 have 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.
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	CT	Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine	Additive effects are caused by PK and PD interactions between diltiazem and ivabradine. Both diltiazem and ivabradine are heart rate lowering substances. Moreover, diltiazem increases ivabradine exposure (2 to 3 fold increase in AUC) through CYP 3A4 inhibition. This could lead to an exacerbated reduction in patient's heart rate (see 2 CONTRAINDICATIONS).

Agent	Source on Evidence	Effect	Clinical comment
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 plasma concentration. It is recommended that the phenytoin plasma 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 coadministered 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	CT	↑ simvastatin exposure	The concomitant administration of diltiazem with statin drugs warrants caution, and requires close medical supervision. Rhabdomyolysis and hepatitis have been reported in patients treated with atorvastatin or simvastatin in

Agent	Source on Evidence	Effect	Clinical comment
			combination with diltiazem, and in the case of simvastatin-treated patients, deaths have occurred. If diltiazem is prescribed to a patient already taking a statin, consideration should be given to decreasing the dose of the statin. In a published study of 10 healthy volunteers treated with simvastatin 20 mg, after 2 weeks of treatment with diltiazem 240 mg, the mean C_{max} (3.6 - fold) and AUC (5-fold) of simvastatin were increased significantly.
Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)	T	↑ diltiazem plasma concentration	Strong CYP3A4 inhibitors may significantly increase the plasma 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	Cardiovascular effects of an intravenous bolus of an ionic X-ray contrast 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.

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

Other 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

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, lightheadedness, syncope, orthostasis, or tachycardia.

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 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.

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.

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 vasodilatory action.

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.

Hemodynamic and Electrophysiologic Effects

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).

10.2 Pharmacodynamics

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%.

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

diltiazem is bound to plasma proteins. Following extensive hepatic metabolism, only 2-4% of the drug appears unchanged in the urine and 6-7% appears as metabolites.

The metabolic pathways of diltiazem hydrochloride extended-release capsules include N– and O-demethylation (via cytochrome P450), deacetylation (via plasma and tissue esterases), in addition to conjugation (via sulfation and glucuridonation). *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 10-20% of the parent drug and is 25-50% as potent as diltiazem in terms of coronary vasodilation.

Diltiazem Hydrochloride Extended-Release Capsules
When compared to a regimen of immediate-release tablets at steady-state, approximately 93% of drug is absorbed from the diltiazem hydrochloride extended-release capsule formulation. When diltiazem hydrochloride extended-release capsule was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected T_{max}, however, occurred slightly earlier. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 4 to 9.5 hours (mean 6.5 hours).

Diltiazem hydrochloride extended-release capsule demonstrates non-linear pharmacokinetics. As the dose of diltiazem hydrochloride extended-release 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 2.4 times. When the dose is increased from 240 mg to 360 mg there is an increase in AUC of 1.5 times.

In a study with 14 healthy subjects, the steady-state pharmacokinetics of diltiazem hydrochloride extended-release capsules were compared with diltiazem hydrochloride controlled delivery capsule at a dose of 240 mg/day. The bioavailability of diltiazem hydrochloride extended-release capsules relative to diltiazem hydrochloride controlled delivery capsule based on mean diltiazem area under the curve (AUC) was 124% (90% C.I. 111-139%). The relative mean C_{max} was 121%.

***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**

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.

10.3 Pharmacokinetics

Hypertension

In a parallel-group, double-blind placebo-controlled study of 198 patients with mild to moderate essential hypertension, diltiazem hydrochloride extended-release capsule was given for four weeks. The changes in diastolic blood pressure measured at trough (24 hours after the dose) for placebo, 90 mg, 180 mg and 360 mg were -5.4, -6.3, -6.2, -8.2 mmHg, respectively.

Another double-blind placebo-controlled clinical trial in 56 patients with mild to moderate essential hypertension treated for 8 weeks followed a dose-escalation design. Supine diastolic blood pressure measured at trough following two week intervals of treatment with diltiazem hydrochloride extended-release was reduced by -3.7 mmHg with 120 mg/day versus -2.0 mmHg with placebo, by -7.6 mmHg after escalation to 240 mg/day versus -2.3 mmHg with placebo, by -8.1 mmHg after escalation to 360 mg/day versus -0.9 mmHg with placebo.

In a double-blind, multicentre study, 181 patients with mild to moderate essential hypertension were controlled with diltiazem hydrochloride controlled delivery capsule monotherapy, were

randomized to the same dose of either diltiazem hydrochloride controlled delivery capsule or diltiazem hydrochloride extended-release capsule. The least squares mean for the difference in diastolic blood pressure at trough between diltiazem hydrochloride extended-release capsule and diltiazem hydrochloride controlled delivery capsule groups pooled was 0.19 mm Hg (90% confidence interval -1.2 to 1.6 mm Hg). Data based on the same dose comparisons were supportive of this result.

Angina
In a double-blind, parallel group placebo-controlled trial, 158 patients with chronic stable angina were, after titration, treated for 2 weeks on their target maintenance dose of diltiazem hydrochloride extended-release capsule.

Diltiazem hydrochloride extended-release capsule increased exercise tolerance times in a Bruce exercise protocol, at trough, 24 hours after dosing. Exercise tolerance times increased by 14, 26, 41 and 33 seconds for placebo, 120 mg, 240 mg, and 360 mg/day treated patient groups respectively. At peak, 8 hours after dosing, exercise tolerance times were increased by 13, 38, 64 and 53 seconds for placebo, 120 mg, 240 mg and 360 mg/day treated groups, respectively.

11 STORAGE, STABILITY AND DISPOSAL

Store in a tight container between 15°C and 30°C. Protect from light.
Keep out of sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

N/A

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug substance

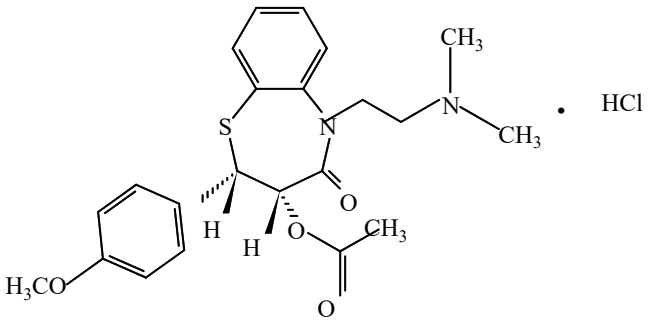
Proper name: Diltiazem Hydrochloride

Chemical name: 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: $C_{22}H_{26}N_2O_4S.HCl$

Molecular mass: 450.98 g/mol

Structural formula:



Physicochemical properties: Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste.

Solubility: It is soluble in water, methanol and chloroform.

14 CLINICAL TRIALS

No clinical trial data available.

14.3 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of ACT Diltiazem T 360 mg extended-release capsules (Teva Canada Limited.) with Tiazac® 360 mg extended-release capsules (Crystaal Division of Biovail Corporation) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 22 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem 1 x 360 mg Geometric Mean Arithmetic mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Mean**	**90% Confidence Interval**
AUC_T (ng·h/mL)	3378.92 3566.1 (33.41)	3333.28 3511.7(32.14)	101.4	95.9 – 107.2
AUC_I (ng·h/mL)	3466.31 3663.5 (33.81)	3470.12 3668.0 (33.21)	99.9	94.5 – 105.6
C_{max} (ng/mL)	216.05 225.90 (31.27)	193.46 204.55 (34.35)	111.7	103.1 – 121.0
T_{max}[3] (h)	7.00 (1.08)	6.00 (1.77)		
$T_{1/2}$ [3] (h)	7.96 (21.20	8.97 (25.45)		

[1] ACT Diltiazem T (diltiazem hydrochloride) extended-release capsules, 360 mg (Teva Canada Limited)
[2] Tiazac® (diltiazem hydrochloride) extended-release capsules, 360 mg (Crystaal Division of Biovail Corporation)
[3] Expressed as the arithmetic mean (CV%) only

A randomized, two-way, single-dose, crossover comparative bioavailability study of ACT Diltiazem T 360 mg extended-release capsules (Teva Canada Limited) with Tiazac® 360 mg extended-release capsules (Crystaal Division of Biovail Corporation) was conducted in healthy, adult, male subjects under high-fat, high-calorie fed conditions. Comparative bioavailability data from the 24 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem 1 x 360 mg Geometric Mean Arithmetic mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	3833.95 3982.6 (27.99)	3837.46 3966.1 (25.40)	99.9	94.3 – 105.8
AUC_I (ng.h/mL)	3906.80 4067.6 (28.90)	3926.32 4064.3 (26.01)	99.5	94.1 – 105.3
C_{max} (ng/mL)	269.22 276.038 (21.74)	261.791 269.098 (22.55)	102.8	96.6 – 109.5
T_{max}[3] (h)	- 6.00 (1.21)	- 6.00 (1.17)		
$T_{½}$[3] (h)	- 7.18 (20.32)	- 7.57 (21.41)		

[1] ACT Diltiazem T (diltiazem hydrochloride) extended-release capsules, 360 mg (Teva Canada Limited)

[2] Tiazac® (diltiazem hydrochloride) extended-release capsules, 360 mg (Crystaal Division of Biovail Corporation)

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

A randomized, two-way, multiple-dose, crossover comparative bioavailability study of ACT Diltiazem T 360 mg extended-release capsules (Sandoz Canada Inc.) with Tiazac® 360 mg extended-release capsules (Crystaal Division of Biovail Corporation), administered as 1 x 360 mg extended-release capsules once a day for seven days, was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 25 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 360 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval

$AUC_{tau,ss}$ (ng.h/mL)	4804.03 5123.09 (41.16)	4790.13 5066.98 (37.70)	100.3	96.4 – 104.3
$C_{max,ss}$ (ng/mL)	344.97 372.413 (44.56)	346.94 367.800 (37.97)	99.4	92.3 – 107.1
$C_{min,ss}$	87.65 95.892 (49.38)	93.26 100.325 (41.61)	94.0	88.6 – 99.7
T_{max}[3] (h)	6.00 (25.73)	5.00 (26.82)		
FL[3](%)	128.88 (17.62)	127.80 (24.71)		

[1] ACT Diltiazem T (diltiazem hydrochloride) extended-release capsules, 360 mg (Teva Canada Limited)
[2] Tiazac® (diltiazem hydrochloride) extended-release capsules, 360 mg (Crystaal Division of Biovail Corporation)
3 Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product**.**

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity

Table 3- Acute Toxicity

Route	Animal	Sex	LD_{50} mg/kg	LD_{50} 95% Confidence Limits (mg/kg)
Oral	Mice Rats	M&F M&F	415 - 700 560 - 810	(343 - 736) (505 - 1004)
S.C	Mice	M&F	260 - 550	(220 - 672)
I.P	Mice Rats	M&F M&F	187 211	(165 - 211) (155 - 287)
I.V	Mice Rats	M&F M&F	58 - 61 38 - 39	(52 - 69) (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 who 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.

Chronic Toxicity/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 Development 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 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 12	Fetal mortality greatly increased when 12.5 mg/kg or more was administered. No teratogenic effect was demonstrated.
Intra-peritoneal	Single dose 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.

Table 5 - Results in Rats

Route	Doses mg/kg	Time of Administration During gestation	Findings in the offspring
Oral	10, 30, 100	Day 6 to 15	No teratogenic effect.
Oral	Single doses of 300, 400, 600	On one of days 9 to 14	Significant incidence of skeletal malformations involving vertebrae and 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 and 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 doses of 80 Single doses of 40	One of days 9 to 14 One of days 11 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 and 14. Vertebral column deformities were induced when 80 mg/kg was administered on day 11. No teratogenic effect.

Table 6- Results in Rabbits

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring

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 PO. 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 post-partum. 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrTIAZAC®, Extended-Release Capsules, 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg, submission control 266363, Product Monograph, Bausch Health, Canada Inc. December 21, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ACT Diltiazem T
Diltiazem Hydrochloride Extended-Release Capsules, Manufacturer's Standard

Read this carefully before you start taking **ACT Diltiazem T** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ACT Diltiazem T.**

What is ACT Diltiazem T used for?
ACT Diltiazem T is used in adults to:

- treat mild to moderate high blood pressure.

- 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. ACT Diltiazem T is normally used in patients who have tried other treatments for their chest pain, but did not receive benefits, or had bad side effects.

How does ACT DILTIAZEM T work ?

ACT Diltiazem T belongs to the group of drugs called "calcium channel blockers" or "calcium antagonists".

- ACT Diltiazem T relaxes the arteries, which allows blood to flow freely through them. This helps to lower blood pressure.

- ACT Diltiazem T reduces the amount of oxygen that your heart muscle needs. This helps control chest pain.

What are the ingredient in ACT Diltiazem T?
Medicinal ingredients: Diltiazem Hydrochloride

Non-medicinal ingredients: Ethylcellulose, Gelatin, Hydroxypropyl Methylcellulose, Magnesium Stearate, Polymethacrylate, Polysorbate, Povidone, Sugar Spheres, Talc and Titanium Dioxide.

ACT Diltiazem T also contains one or more of the following dyes: Black Iron Oxide (180 mg and 300 mg), D&C Red #28 (120 mg, 240 mg and 300 mg), FD&C Blue #1 (120 mg, 240 mg and 300 mg), FD&C Green #3 (180 mg, 240 mg and 360 mg).

ACT Diltiazem T comes in the following dosage forms:

Extended-release capsules: 120 mg, 180 mg, 240 mg, 300 mg and 360 mg.

Do not use ACT Diltiazem T if:

- you are allergic to diltiazem or any other ingredients in ACT Diltiazem T or its container.
- you have heart rhythm disorders and do not have a pacemaker
- you have very low blood pressure (less than 90 mmHg systolic).
- you have very slow heartbeat (less than 40 beats/minutes).
- 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 ACT Diltiazem T.
- 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 take ACT Diltiazem T. 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 high blood sugar or diabetes.
- are at risk of developing an intestinal obstruction
- are 65 years of age or older.
- have a history of heart failure, new shortness of breath, slow heartbeat or low blood pressure. Cases of kidney injury in patients with such conditions have been reported.
- have asthma or other breathing problems. ACT Diltiazem T may cause your symptoms to get worse after a dose increase.

Other warnings you should know about:

ACT Diltiazem T can cause serious side effects, including:

• **Kidney problems:** ACT Diltiazem T 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): ACT Diltiazem T may affect your blood sugar. If you have diabetes, closely monitor your blood sugar while taking ACT Diltiazem T 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 ACT Diltiazem T. 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 ACT Diltiazem T.
- If you take ACT Diltiazem T 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 ACT Diltiazem T and tell your healthcare professional **right away**.

Breastfeeding: ACT Diltiazem T passes into breast milk and may harm your baby. Do not breastfeed during treatment with ACT Diltiazem T. 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 ACT Diltiazem T. 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 ACT Diltiazem T 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.
- ACT Diltiazem T 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 ACT Diltiazem T 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.

Taking ACT Diltiazem T 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 interact with ACT Diltiazem T:

- 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, phenobarbital, phenytoin;
- 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.

<u>Alcohol</u>

Drinking alcohol while taking ACT Diltiazem T 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 doctor if you experience dizziness, light-headedness, fainting, decreased blood pressure or increased heart rate.

<u>Grapefruit juice</u>

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

How to take ACT Diltiazem T:

- Take ACT Diltiazem T exactly as your healthcare professional tells you.

- ACT Diltiazem T is taken once a day at about the same time every day.
- DO NOT chew or crush ACT Diltiazem T capsules.

Usual Dose:
High Blood Pressure: the usual starting doses 180 to 240 mg once a day. 120 mg a day may be used in some patients. Maximum dose**:** 360 mg a day.

Chest Pain (angina): your doctor will decide the best dose for you. The usual starting dose is 120 mg to 180 mg once a day. Your dose may be slowly increased (over 7 to 14 days) up to 360 mg once a day.

Overdose:

Signs of an overdose with ACT Diltiazem T 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 ACT Diltiazem T, contact healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and take your next dose as scheduled. Do not take two doses at the same time.

What are possible side effects from using ACT Diltiazem T?
These are not all the possible side effects you may feel when taking ACT Diltiazem T. If you experience any side effects not listed here, tell your healthcare professional.

- Headache, dizziness, malaise;
- Nausea (feeling like vomiting);
- Flushing (facial redness) or feeling unusually warm;
- Rash;
- Temporary swelling;
- 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		✓	
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		✓	

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**	
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	✓		
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			✓

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**	
Heart Failure: shortness of breath, 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, 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 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		✓	

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**	
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 ACT Diltiazem T capsules in tight containers between 15°C and 30°C. Protect from light. Keep out of reach and sight of children.

If you want more information about ACT Diltiazem T:

- 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 http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited Toronto, Ontario M1B 2K9

Last revised: September 08, 2023