PRODUCT MONOGRAPH

PrTIAZAC® XC

(Diltiazem Hydrochloride)

Extended-Release Tablets

120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

Antihypertensive / Antianginal Agent

Name:
Valeant Canada LP

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(Diltiazem HCl)
Extended- Release Tablets
Antihypertensive / Antianginal Agent

PART 1: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Summary Product Information

Route of Administration	Dosage Form/Strength	Nonmedicinal Ingredients
Oral	Tablets: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg	Carnauba wax, colloidal silicone dioxide, croscarmellose sodium, eudragit, hydrogenated vegetable oil, hydroxypropylmethylcellulose, magnesium stearate, microcrystalline cellulose, microcrystalline wax, polydextrose, polyethylene glycol, polysorbate, povidone, pregelatinized starch, simethicone, sodium starch glycolate, sucrose stearate, talc, and titanium dioxide.

For Complete Information see Dosage Forms, Composition and Packaging Sections

INDICATIONS AND CLINICAL USE

Essential Hypertension:
For the treatment of mild to moderate essential hypertension. It is to be administered once daily at bedtime.

TIAZAC® XC (diltiazem hydrochloride) should normally be used in those patients in whom treatment with diuretics or beta-blockers has been ineffective, or has been associated with unacceptable adverse effects.

The safety of concurrent use of TIAZAC XC with other antihypertensive agents has not been established.

No morbidity and mortality studies have been carried out to support the use of TIAZAC XC (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics SECTION).

Chronic Stable Angina:
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.

TIAZAC XC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, these patients must be monitored closely (See Warnings and Precautions).

Since the safety and efficacy of TIAZAC XC in the management of unstable or vasospastic angina has not been substantiated, its use for these conditions is not recommended.

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.

Pediatrics
Safety and efficacy in children has not been studied.

CONTRAINDICATIONS
TIAZAC XC (diltiazem hydrochloride) is contraindicated:

- In patients with sick sinus syndrome, except in the presence of an implanted pacemaker;
- In patients with second or third-degree AV block, except in the presence of an implanted pacemaker;
- In patients with known hypersensitivity to diltiazem;
- 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. Fetal malformations and adverse effects on pregnancy have been reported in animals.
- Concomitant use of dantrolene.
- Concomitant use of ivabradine.

WARNINGS AND PRECAUTIONS

Cardiac Conduction
TIAZAC XC (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 cardiac failure (see also 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.

Postinfarction patients with reduced ejection fraction are at particular risk for subsequent heart failure when treated with diltiazem. Accordingly, diltiazem should be avoided in patients with substantially reduced ejection fraction.

Hypotension
Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

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.

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 a sustained-release formulation of diltiazem in acute myocardial infarction, their use may have effects similar to those of immediate-release dilitazem in acute myocardial infarction.

Acute Hepatic Injury
In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, AST, ALT and symptoms consistent with 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 ADVERSE REACTIONS). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

Use with Beta-Blockers
Generally, diltiazem should not be given to patients with impaired left ventricular function if they are already receiving beta-blockers. 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 under close medical supervision.

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.

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.

Special Populations:

Impaired Hepatic or Renal Function
Because TIAZAC XC (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 severe hepatic or renal function (see ADVERSE REACTIONS).

Pediatrics:
Safety and effectiveness in children has not been studied.

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

Use in the Elderly
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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In clinical trials with 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%).

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hypertension: Table 2 presents the most common adverse reactions reported in the placebo-controlled hypertension trials in patients receiving a diltiazem hydrochloride extended-release formulation (once-a-day dosing) up to 360 mg.

Table 2 Adverse Events >1%:
Diltiazem Hydrochloride Extended-Release Formulation
Once-a-day PM Administration
Placebo-Controlled Hypertension Trials

Adverse Reactions	Placebo n=69 # pts (%)	Diltiazem Hydrochloride Extended-Release 120-360 mg n=238 # pts (%)
Headache	10 (15)	29 (12)
Oedema lower limb	4 (6)	9 (4)
Upper respiratory tract infection	2 (3)	12 (5)
Nasopharyngitis	1 (1)	7 (3)
Sinusitis	2 (3)	7 (3)

Angina:
In the angina clinical study, the adverse event profile of TIAZAC XC was consistent with that previously described for TIAZAC XC and other formulations of diltiazem HCl. The most frequent adverse effects experienced by TIAZAC XC patients are presented in Table 3.

Table 3 Adverse Events >1%:
Diltiazem Hydrochloride Extended-Release Formulation
Once-a-day Administration
Placebo-Controlled Angina Trial

Adverse Reactions	Placebo n=61 # pts (%)	Diltiazem Hydrochloride Extended-Release 180, 360 & 420 mg n=250 # pts (%)
Oedema Lower Limb	2 (3.3)	17 (6.8)
Dizziness	0 (0)	16 (6.4)
Fatigue	3 (4.9)	12 (4.8)
Bradycardia	0 (0)	9 (3.6)
Atrioventricular Block First Degree	0 (0)	8 (3.2)
Cough	0 (0)	5 (2.0)

Uncommon Clinical Trial Adverse Drug Reactions (< 1%)

The following data is divided into two sections. The first represents ADRs <1% in TIAZAC XC Clinical trials. The second reflects ADRs <1% in other diltiazem products.

The following treatment related adverse drug reactions were reported with <1% incidence in the TIAZAC XC clinical trial:

Cardiac disorders: Atrioventricular block (first, degree), palpitations.

Eye disorders: Vitreous floaters, diplopia.

Gastrointestinal disorders: Dyspepsia, nausea.

General disorders and administration site conditions: Feeling jittery, joint swelling, lethargy, neck swelling, oedema NOS, peripheral swelling, swelling NOS.

Investigations: Aspartate aminotransferase increased.

Nervous system and psychiatric disorders: Dizziness (vertigo), sinus headache.

Renal and urinary disorders: Urinary frequency.

Respiratory, thoracic and mediastinal disorders: Dyspnoea NOS.

Skin and subcutaneous disorders: Dermatitis NOS, erythema NEC, face oedema, pruritus NOS, rash generalized.

Vascular disorders: Flushing.

The following adverse events were reported with a frequency <1% in other diltiazem products:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure (left ventricular dysfunction), 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 Hepatic WARNINGS), CPK increase.

Metabolism and nutrition disorders: Hyperglycemia, hyperuricemia.

Nervous System and psychiatric disorders: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, 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

Post-Marketing Surveillance

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 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 TIAZAC therapy is yet to be established.

DRUG INTERACTIONS

Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P450 system. Coadministration of diltiazem with other drugs which follow the same route of biotransformation may result in altered bioavailability. 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.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, and warfarin. Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, and rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, and theophylline.

Table 4- Established or Potential Drug-Drug Interactions

Agent	Ref	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.

Table 4- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
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 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 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 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 carbamazepine and/or diltiazem may be necessary.

Table 4- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
Anti-H2 agents (Cimetidine, ranitidine)	CT	↑ cimetidine, ranitidine exposure	A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma C_{max} levels (58%) and area-under-the-curve AUC (53%) after a 1-week course of cimetidine 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 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 CONTRAINDICATIONS).

Table 4- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
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.
Erythromycin	CT	↑ erythromycin exposure	The use of erythromycin should be avoided in patients treated with CYP3A inhibitors, including diltiazem. An analysis reported in the literature indicates that the risk of sudden death is increased in current users of erythromycin (incidence-rate ratio = 2.01; 95% CI= 1.08 to 3.75), and this risk is further elevated in concurrent users of CYP3A inhibitors (5.35; 95% CI= 1.72 to 16.64), including diltiazem. Cohort analysis revealed one death in 106 person - years in diltiazem-treated patients.
Ivabradine	CT	Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine	Avoid concomitant use of moderate CYP3A4 inhibitors such as diltiazem and verapamil when using 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 CONTRAINDICATIONS).
Lithium	T	↑ Lithium neurotoxicity	Risk of increased in lithium-induced neurotoxicity.
Other antiarrhythmic agents	T	↑ antiarrhytmic 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.

Table 4- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
Rifampicin	CT	↓ diltiazem plasma concentration	Administration of diltiazem with rifampin 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 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.
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

Drug-Food Interactions

Alcohol:
Alcohol can exhibit hypotensive effects. Coadministration 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 coadministration with calcium products.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
TIAZAC XC (diltiazem hydrochloride) has an extended-release delivery system designed to deliver maximum effect in the morning when administered at night-time. Accordingly, TIAZAC XC should be administered once daily at bedtime. TIAZAC XC should not be chewed or crushed. TIAZAC XC may be taken with or without food, but should be so taken consistently.

Recommended Dose and Dose Adjustment

Hypertension:
When used as monotherapy, usual starting doses for hypertension are 180 to 240 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 TIAZAC XC or concomitant antihypertensive agents may need to be adjusted when adding one to the other. See WARNINGS and PRECAUTIONS regarding use with beta-blockers.

Angina:
Dosage should be based on individual patient response. Treatment should start with 180 mg once daily; this may be increased at intervals of 7 to 14 days if adequate response is not obtained. Higher

doses may not result in greater anti-anginal effect. The maximum dose is 360 mg once daily.

TIAZAC XC may be safely co-administered with short- and long-acting nitrates.
Sublingual nitroglycerin may be taken as required to support acute anginal attacks during TIAZAC XC therapy.

OVERDOSAGE

Significant diltiazem overdose causes cardiovascular and systemic toxicity and may be fatal. The onset of toxicity may be delayed in patients who have ingested a sustained release preparation such as TIAZAC XC. The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse and acute kidney injury, sinus bradycardia with or without isorhythmic dissociation, sinus arrest, atrioventricular conduction disturbances and cardiac arrest. Mental status will often be preserved although patients with hypotension may be drowsy or comatose. Hypoxia may be due to non-cardiogenic lung injury caused by precapillary vasodilation. Impaired gut motility may result in ileus. Patients are often hyperglycemic due to impaired insulin release. Fatalities may occur with large overdoses and in patients with coexisiting cardiac disease or with cardiotoxic coingestants.

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

Severely symptomatic patients poisoned with diltiazem should receive supplemental oxygen and be stabilized in the usual fashion with attention to maintaining the airway and restoring circulation. An electrocardiogram and routine blood analysis including electrolytes, glucose, and the usual search for coingestants should be performed.

Induced emesis is contraindicated. Patients who present within an hour of a significant overdose of diltiazem should have gastric lavage followed by activated charcoal. Lavage is not indicated for patients with delayed presentations. Whole bowel irrigation may be considered in patients with significant ingestions of sustained-release diltiazem.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia:
Atropine and intravenous fluids may suffice in patients with mild poisoning.

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:
Calcium salts given intravenously (should be avoided in patients who may have coingested digoxin).

Catecholamine pressors may be used to improve cardiac contractility (epinephrine, dopamine, dobutamine, isoproterenol) or vascular tone (norepinephrine, epinephrine, dopamine). High dose insulin together with glucose or glucagon may be effective in patients not responding to catecholamines.

Sustained release calcium channel blockers may cause delayed onset of toxicity and once established, toxicity may last for several days. Patients who have symptoms following a TIAZAC XC ingestion should be treated and monitored until all signs and symptoms of toxicity have resolved. Patients who remain asymptomatic with normal vital signs during a 24 hour period of observation in a monitored setting may be discharged.

ACTION AND CLINICAL PHARMACOLOGY

TIAZAC XC (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (calcium channel blocker or calcium channel antagonist) of the benzothiazepine (non-dihydropyridine) class.

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 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.

Pharmacodynamics

Hypertension:

In a double-blind clinical study, a diltiazem hydrochloride extended-release clinical trial formulation with the same bead coating as TIAZAC XC, administered daily at night for 7 weeks at doses of 120

mg, 240 mg, 360 mg and 540 mg was compared to administration of 360 mg in the morning. The 540 mg dose is not approved for use in Canada.

Group mean reductions in diastolic blood pressure between 6AM and 12 NOON, as measured by ambulatory blood pressure monitoring (ABPM) for 120 mg, 240 mg, 360 mg and 540 mg taken at night were 4.7, 8.9, 10.2 and 14.8 mm Hg, respectively, placebo-corrected. These reductions in diastolic blood pressure for all doses were significantly different from placebo and dose-related. Within this time period of 6 AM to 12 NOON, the 360 mg PM dose produced a statistically significant 3.3 mm Hg greater reduction in diastolic blood pressure than the 360 mg AM dose.
When changes in mean seated office diastolic blood pressure from baseline were evaluated at 8 AM, the following decreases were noted: placebo 6.6 mmHg; 120 mg PM 10.5 mmHg; 240 mg PM 13.1 mmHg; 360 mg PM 15.5 mmHg; 540 mg PM 20.3 mmHg, with $p<0.0001$ for all comparisons with corresponding baseline measurements. For 360 mg AM, a mean decrease from baseline of 10.8 mmHg was seen, $p<0.0001$. When measured at 6 PM, the following decreases were noted: placebo 5.5 mmHg; 120 mg PM 5.2 mmHg; 240 mg PM 8.7 mmHg; 360 mg PM 10.3 mmHg; 540 mg PM 14.1 mmHg, with $p<0.0001$ for all comparisons with corresponding baseline measurements. For 360 mg AM, a mean decrease from baseline of 13.1 mmHg was seen, $p<0.0001$.

Angina:
In a double-blind study involving 311 patients with chronic stable angina, evening doses of 180, 360 and 420 mg clinical trial formulation of TIAZAC XC were compared to placebo and to 360 mg administered in the morning. The 420 mg dose is not approved for use in Canada. All doses administered at night increased exercise tolerance when compared with placebo after 21 hours, during the diltiazem trough period. The median effect, placebo-subtracted, was 20 to 28 seconds for all three doses; no dose-response was demonstrated, i.e., use of the higher doses tested did not consistently result in increased exercise tolerance. The 360 mg dose given in the morning also improved exercise tolerance when measured 25 hours later. As expected, the effect was smaller than the effects measured only 21 hours following nighttime administration. TIAZAC XC had a larger effect in increasing exercise tolerance at peak serum concentrations than at trough.

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 atrio-His conduction time and atrioventricular 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 WARNINGS). In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Pharmacokinetics

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 range of 50-200 ng/mL. *In-vitro* human serum binding studies revealed that 70 to 80% of diltiazem is bound to plasma proteins. The pharmacokinetics of diltiazem are non-linear.

Metabolism:

The metabolic pathways of diltiazem 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 active 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.

Excretion:

Following extensive hepatic metabolism, only 2-4% of the drug appears unchanged in the urine and 6-7% appears as metabolites.

TIAZAC XC Tablets: TIAZAC XC has an extended-release delivery system designed for night-time administration, resulting in maximum diltiazem plasma levels in the morning.

Administration of TIAZAC XC tablets in the fasted state at bedtime, in a single study, resulted in detectable diltiazem plasma levels after 3 to 4 hours, and peak plasma levels between 11 and 18 hours post dose. After single dosing, diltiazem bioavailability ranged from 2.5% to 16% over the first six hours. The apparent elimination half-life for TIAZAC XC after single or multiple dosing is 6 to 9 hours.

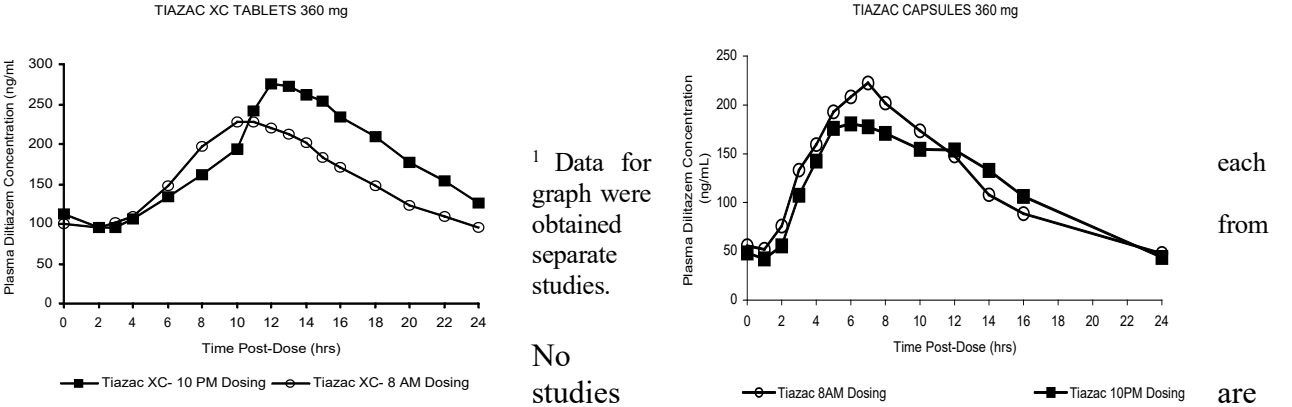
When a single dose of 360 mg TIAZAC XC tablets, administered at night, was compared to the same dose given in the morning, an 18% greater systemic exposure and 11% higher peak exposure were observed at night relative to morning. Under steady-state conditions, night-time administration resulted in 22% and 16% greater systemic and peak exposure, respectively, relative to morning administration.

When single doses of 360 mg TIAZAC XC tablets were given in the morning to assess potential food interaction, the observed ratios of means were $AUC_{\tau ao}$ 112.4% (90% C.I. 101.2 - 124.9) and C_{max} 104.0% (90% C.I. 92.9 - 116.5) for the fed/fasted comparison (see DOSAGE AND ADMINISTRATION).

While both TIAZAC XC tablets and TIAZAC capsules possess the same immediate release diltiazem-containing bead cores, the release-controlling polymer bead coatings are different, resulting in different bioavailability profiles. Further, the TIAZAC beads are encapsulated in gelatin capsules to produce the TIAZAC formulation, while TIAZAC XC tablet beads are blended with inert wax beads and excipients, then compressed into tablets.

Diltiazem time course kinetics, as noted across studies in healthy volunteers that evaluated TIAZAC XC tablets and TIAZAC capsules respectively, are presented below in Figure 1.

Figure 1: 24- hour diltiazem plasma concentration time course at steady-state[1]



[1] Data for each graph were obtained from separate studies.

No studies are available that compare the relative bioavailability of TIAZAC XC tablets to TIAZAC capsules directly.

Special Populations and Conditions

Pediatrics:

Pharmacokinetic studies with TIAZAC XC in children have not been conducted.

Geriatrics:

Pharmacokinetic studies with TIAZAC XC in geriatrics have not been conducted. However it is known that 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.

Sex:

In pharmacokinetic studies in healthy volunteers, there were no statistically significant differences between male and female subjects with respect to the AUC (p=0.099) and C_{max} (p=0.295).

Race:
The effect of race in pharmacokinetic studies has not been evaluated.

Hepatic Insufficiency:
No pharmacokinetic studies have been conducted with TIAZAC XC in patients with hepatic insufficiency.

Renal Insufficiency:
No pharmacokinetic studies have been conducted with TIAZAC XC in patients with renal insufficiency.

STORAGE AND STABILITY

Store at room temperature (15 - 30ºC)
Avoid excessive humidity, and temperatures above 30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TIAZAC XC tablets are available in 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg strengths.

TIAZAC XC tablets contain Diltiazem Hydrochloride. TIAZAC XC also contains: Microcrystalline Cellulose, Eudragit, Povidone, Sucrose Stearate, Magnesium Stearate, Talc, Titanium Dioxide, Hydroxypropylmethylcellulose, Polysorbate, Simethicone, Microcrystalline Wax, Pregelatinized Starch, Sodium Starch Glycolate, Croscarmellose Sodium, Colloidal Silicone Dioxide, Hydrogenated Vegetable Oil, Polydextrose, Polyethylene glycol, Carnauba wax.

TIAZAC XC (diltiazem hydrochloride) Extended-Release Tablets are available in the following strengths. Each white, film coated tablet is debossed with “B” on one side, and the strength on the other.

TIAZAC XC 120 mg tablets are supplied in bottles of 90.
TIAZAC XC 180 mg tablets are supplied in bottles of 90.
TIAZAC XC 240 mg tablets are supplied in bottles of 90.
TIAZAC XC 300 mg tablets are supplied in bottles of 90.
TIAZAC XC 360 mg tablets are supplied in bottles of 90.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

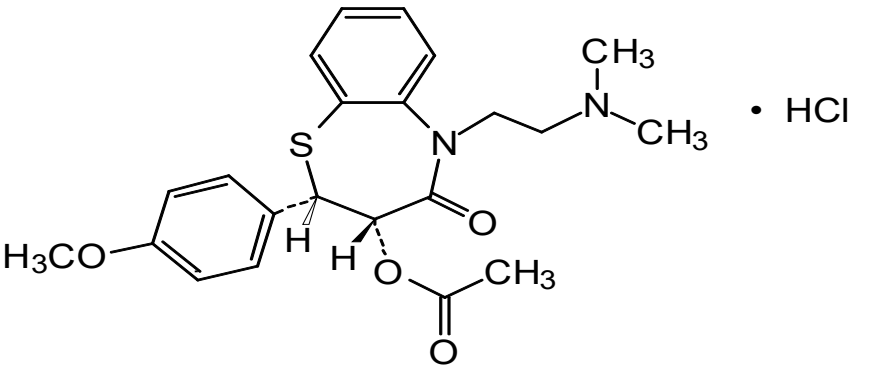
Drug Substance

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 and Molecular Mass: $C_{22}H_{26}N_2O_4S \cdot HCl$ MW 450.98

Structural formula:



Physiochemical Properties:

Diltiazem hydrochloride is a white crystalline powder with a molecular formula of $C_{22}H_{26}N_2O_4S.HCl$ and MW of 450.98. Melting point is 210°C to 215°C. Diltiazem hydrochloride is freely soluble in water, chloroform, formic acid and methanol. It is sparingly soluble in dehydrated alcohol, and insoluble in ether. The pH is of diltiazem is 4.3 to 5.3 (1% solution). The pKa value is 7.7.

TIAZAC XC tablets are a modified release dosage form that contain 120 mg, 180 mg, 240 mg, 300 mg, or 360 mg of diltiazem hydrochloride.

CLINICAL TRIALS

Study Demographics and Trial Design

One clinical study was conducted in subjects with mild to moderate hypertension, and another clinical study was conducted in subjects with chronic stable angina.

Table 5

Trial Design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (range)	Gender
Hypertension Double-blind, placebo-controlled, randomized, parallel group, dose-response.	Tablet, oral, 13 weeks	478 randomized, 429 completers	52.2 years (26 to 75 years)	63.4% male
Angina Double-blind, placebo-controlled, randomized, parallel-group, multicenter, dose-response	Tablet, oral, 3 weeks	311 randomized, 296 completers	63.2-65.4 per treatment group (33-84 years)	73.8-88.7% males treatment group

Hypertension:

In a double-blind clinical study, a diltiazem hydrochloride extended-release clinical trial formulation with the same bead coating as TIAZAC XC, administered daily at night for 7 weeks at doses of 120 mg, 240 mg, 360 mg and 540 mg was compared to administration of 360 mg in the morning. The 540 mg dose is not approved for use in Canada.

Group mean reductions in diastolic blood pressure between 6 AM and 12 NOON, as measured by ambulatory blood pressure monitoring (ABPM) for 120 mg, 240 mg, 360 mg and 540 mg taken at night were 4.7, 8.9, 10.2 and 14.8 mm Hg, respectively, placebo-corrected. These reductions in diastolic blood pressure for all doses were significantly different from placebo and dose-related. Within this time period of 6 AM to 12 NOON, the 360 mg PM dose produced a statistically significant 3.3 mm Hg greater reduction in diastolic blood pressure than the 360 mg AM dose.

When changes in mean seated office diastolic blood pressure from baseline were evaluated at 8 AM, the following decreases were noted: placebo 6.6 mmHg; 120 mg PM 10.5 mmHg; 240 mg PM 13.1 mmHg; 360 mg PM 15.5 mmHg; 540 mg PM 20.3 mmHg, with $p<0.0001$ for all comparisons with corresponding baseline measurements. For 360 mg AM, a mean decrease from baseline of 10.8 mmHg was seen, $p<0.0001$. When measured at 6 PM, the following decreases were noted: placebo 5.5 mmHg; 120 mg PM 5.2 mmHg; 240 mg PM 8.7 mmHg; 360 mg PM 10.3 mmHg; 540 mg PM 14.1 mmHg, with $p<0.0001$ for all comparisons with corresponding baseline measurements. For 360 mg AM, a mean decrease from baseline of 13.1 mmHg was seen, $p<0.0001$.

Angina:

In a double-blind study involving 311 patients with chronic stable angina, evening doses of 180, 360

and 420 mg clinical trial formulation of TIAZAC XC were compared to placebo and to 360 mg administered in the morning. The 420 mg dose is not approved for use in Canada. All doses administered at night increased exercise tolerance when compared with placebo after 21 hours, during the diltiazem trough period. The median effect, placebo-subtracted, was 20 to 28 seconds for all three doses; no dose-response was demonstrated, i.e., use of the higher doses tested did not consistently result in increased exercise tolerance. The 360 mg dose given in the morning also improved exercise tolerance when measured 25 hours later. As expected, the effect was smaller than the effects measured only 21 hours following nighttime administration. TIAZAC XC had a larger effect in increasing exercise tolerance at peak serum concentrations than at trough.

Comparative Bioavailability
TIAZAC XC has an extended-release delivery system designed for night-time administration, resulting in maximum diltiazem plasma levels in the morning.

Administration of TIAZAC XC tablets in the fasted state at bedtime, in a single study, resulted in detectable diltiazem plasma levels after 3 to 4 hours, and peak plasma levels between 11 and 18 hours post dose. After single dosing, diltiazem bioavailability ranged from 2.5% to 16% over the first six hours. The apparent elimination half-life for TIAZAC XC after single or multiple dosing is 6 to 9 hours.

When a single dose of 360 mg TIAZAC XC tablets, administered at night, was compared to the same dose given in the morning, an 18% greater systemic exposure and 11% higher peak exposure were observed at night relative to morning. Under steady-state conditions, night-time administration resulted in 22% and 16% greater systemic and peak exposure, respectively, relative to morning administration.

When single doses of 360 mg TIAZAC XC tablets were given in the morning to assess potential food interaction, the observed ratios of means were $AUC_{\tau ao}$ 112.4% (90% C.I. 101.2 - 124.9) and C_{max} 104.0% (90% C.I. 92.9 - 116.5) for the fed/fasted comparison (see DOSAGE AND ADMINISTRATION).

DETAILED PHARMACOLOGY

***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 g/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.

TOXICOLOGY

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	187211	(165-211)
	Rats	M&F		(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 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.

REPRODUCTION STUDIES
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.

Results in Rats

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring
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 300, 400, 600	On one of days 9 to 14	Significant incidence of skeletal 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 doses 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.

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 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 to 18 of gestation aborted; at 35 mg/kg, a significant increase in skeletal malformations was recorded in the offspring.

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 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.

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PART III: CONSUMER INFORMATION
TIAZAC®XC
Diltiazem hydrochloride Extended-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when TIAZAC®XC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TIAZAC XC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TIAZAC XC is used for the treatment of angina (chest pain) and mild to moderate high blood pressure. TIAZAC XC should normally be used in those patients in whom treatment with other blood pressure reduction medications has been ineffective, or have been associated with unacceptable side effects.

What it does:
TIAZAC XC belongs to a group of drugs called "calcium channel blockers" or "calcium antagonists".
TIAZAC XC relaxes the arteries, thereby lowering blood pressure.
TIAZAC XC increases the supply of oxygen to heart muscle, thereby controlling chest pain.

When it should not be used:
Do not use TIAZAC XC if you:
- are pregnant or plan to become pregnant.
- are breastfeeding
- have a known allergy to diltiazem or any of the non-medicinal ingredients in TIAZAC XC.
- have very low blood pressure (<90 mmHg systolic).
-have a very slow heart beat (40 beats/min or less).
-have heart rhythm disorders and do not have a pacemaker.
- have severe heart failure with fluid in the lungs**.**
-are taking a medicine called dantrolene used for severe muscle spasms or severe fever.
- are taking a medicine called ivabradine used for heart failure.

What the medicinal ingredient is:
Diltiazem Hydrochloride

What the nonmedicinal ingredients are:
Microcrystalline cellulose, polyacrylate dispersion, povidone, sucrose stearate, magnesium stearate, talc, titanium dioxide, hydroxypropylmethylcellulose, polysorbate, simethicone, microcrystalline wax, pregelatinized starch, sodium starch glycolate, croscarmellose sodium, colloidal silicon dioxide, hydrogenated vegetable oil, polydextrose, polyethylene glycol, carnauba wax.

What dosage forms it comes in:
Tablets; 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg

WARNINGS AND PRECAUTIONS

BEFORE you use TIAZAC XC talk to your doctor or pharmacist if you:
- have ever had a bad or unusual reaction to any medicine containing diltiazem in the past.
- have had a recent heart attack.
- have heart, liver or kidney disease.
- have high blood sugar or diabetes.
- are 65 years of age or older.
- have a history of heart failure, new shortness ofbreath, slow heartbeat or low blood pressure. Cases of kidney injury in patients with such conditions have been reported.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines. Additional monitoring of your dose or condition may be needed if you are taking other drugs.

The following may interact with TIAZAC XC:
- Antifungal medications with a name ending in "azole";
- Medications used to control the immune system such as cyclosporine;
- Sleeping pills; such as benzodiazepines (midazolam, triazolam);
- Other blood pressure medications: alpha antagonists, beta blockers;
- Heart medications: amiodarone, digoxin, digitalis, flecanide, niedipine, propafenone, quinidine, verapamil, ivabradine;
- Anaesthetics;
- Lithium and imipramine used for some types of mental illness;
- Drugs that dilate the blood vessels: short and long

acting nitrates;
- Medications used to control seizures: carbamazepine, phenobarbital, phenytoin;
- Warfarin used to prevent blood clots;
- Cholesterol lowering medications: statins;
- Theophylline used for breathing problems;
- Terfenadine or ranitidine used for allergies;
- Medications used to control stomach ulcers such as cimetidine will increase the effects of TIAZAC XC.
- Certain antibiotics should not be taken with TIAZAC XC such as erythromycin, rifampin. Check with your pharmacist.
- Multivitamins with minerals (calcium-containing products);
- Drugs to treat inflammation: corticosteroids, methylprednisolone;
- Dantrolene used for severe muscle spasms or severe fever;
- Acetylsalicylic acid (Aspirin) or antiplatelet drugs;
- X-ray contrast agents.

Alcohol: Drinking alcohol while taking TIAZAC XC may cause low blood pressure when you go from lying or sitting to standing up. This can especially occur after the first dose and when the dose is increased. Tell your doctor if you experience dizziness, lightheadedness, fainting decreased blood pressure or increased heart rate.

Grapefruit juice: Drinking grapefruit juice while taking TIAZAC XC may cause headache, irregular heartbeat, edema (swelling), unexplained weight gain and chest pain. Tell your doctor if this happens to you.

PROPER USE OF THIS MEDICATION

TIAZAC XC is taken once daily at bedtime.
TIAZAC XC can be taken with or without food, but should be so taken consistently.
It is important to take TIAZAC XC at night, at approximately the same time.
Tablets are not to be chewed or crushed.

Usual Adult Dose:
High Blood Pressure:
Usual starting dose: 180 mg to 240 mg once a day.
Maximum daily dose: 360 mg once a day.

Chest Pain (angina):
Dosage should be individualized.
Usual starting dose: 180 mg once a day.
Dosage may be slowly increased over 7 to 14 days.
Maximum daily dose: 360 mg once a day.

Overdose:

If you think you have taken too much TIAZAC XC, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

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

TIAZAC XC can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
	Only if severe	**In all cases**	
Common			
Low blood pressure: dizziness, fainting, light-headedness May occur when you go from lying or sitting to standing up.	√		
Peripheral edema: swelling of the ankles	√		
Respiratory tract infection: runny nose, sore throat		√	
Fast, slow or irregular heartbeat		√	
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Uncommon			
Depression: low mood, lack of interest in usual activities, change in sleep and appetite	√		
Heart block: a disease in the electrical system of the heart causing lightheadedness, fainting and irregular heartbeat			√
Angina: chest pain		√	
Heart failure: shortness of breath, leg swelling, an inability to tolerate exercise		√	
Eye problems: decreased vision, irritation, sore red eyes	√		
Increased blood sugar: frequent urination, thirst, and hunger	√		
Rare			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
	Only if severe	**In all cases**	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Serious skin reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Hypersensitivity Syndrome): any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint pain, yellowing of the skin or eyes, dark urine			√

This is not a complete list of side effects. For any unexpected effects while taking TIAZAC XC, contact your doctor or pharmacist.

HOW TO STORE IT

Store tablets at room temperature. Avoid excessive humidity and temperatures above 30°C. **Keep out of sight and reach of children.**

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-product/med-effect-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 healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor:

Valeant Canada LP
2150 St-Elzear Blvd., West
Laval, QC, H7L 4A8
1-800-361-4261

This leaflet was prepared by Valeant Canada LP

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