PRODUCT MONOGRAPH

[Pr] Taro-Diltiazem T

Diltiazem Hydrochloride Extended-Release Capsules, USP

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

Antihypertensive/Antianginal agent

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ACTION AND CLINICAL PHARMACOLOGY

Taro-Diltiazem T (Diltiazem Hydrochloride) is a calcium ion cellular influx inhibitor (calcium entry blocker or calcium ion antagonist).

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 WARNINGS). In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Pharmacokinetics
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 to 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 Taro-Diltiazem T 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 capsules formulation. When Diltiazem Hydrochloride Extended-Release capsules was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected Tmax, 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 capsules demonstrates non-linear pharmacokinetics. As the dose of Diltiazem Hydrochloride Extended-Release capsules 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%.

Pharmacodynamics

Hypertension: In a parallel-group, double-blind placebo-controlled study of 198 patients with mild to moderate essential hypertension, Diltiazem Hydrochloride Extended-Release capsules 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 mm Hg, 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 capsules was reduced by -3.7 mm Hg with 120 mg/day versus -2.0 mm Hg with placebo, by -7.6 mm Hg after escalation to 240 mg/day versus -2.3 mm Hg with placebo, by -8.1 mm Hg after escalation to 360 mg/day versus -0.9 mm Hg with placebo.

In a double-blind, multicenter study, 181 patients with mild to moderate essential hypertension 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 capsules. The least squares mean for the difference in diastolic blood pressure at trough between Diltiazem Hydrochloride Extended-Release capsules 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 capsules.

Diltiazem Hydrochloride Extended-Release capsules 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.

INDICATIONS AND CLINICAL USE

Essential Hypertension: Taro-Diltiazem T (Diltiazem Hydrochloride) is indicated for the treatment of mild to moderate essential hypertension. Taro-Diltiazem T 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.

Taro-Diltiazem T can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Safety of concurrent use of Taro-Diltiazem T with other antihypertensive agents has not been established.

Chronic Stable Angina: Taro-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.

Taro-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 WARNINGS - Use with Beta-Blockers).

Since the safety and efficacy of Taro-Diltiazem T in the management of unstable or vasospastic angina has not been substantiated, its use for these indications is not recommended.

CONTRAINDICATIONS

Taro-Diltiazem T 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 myocardial infarction patients, who have left ventricular failure manifested by congestion;
  In pregnancy and in women of child-bearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals. In repeated dose studies a high incidence of vertebral column malformations were present in the offspring of mice receiving more than 50 mg/kg of diltiazem hydrochloride orally.
  In the offspring of mice receiving a single oral dose of 50 or 100 mg/kg on day 12 of gestation, the incidence of cleft palate and malformed extremities was significantly higher. Vertebral malformations were most prevalent when they received the drug on day 9. In rats, a significantly higher fetal death rate was present when 200 and 400 mg/kg were given orally on days 9 to 14 of gestation. Single oral dose studies in rats resulted in a significant incidence of skeletal malformations in the offspring of the group receiving 400 mg/kg on day 11. In rabbits, all pregnant dams receiving 70 mg/kg orally from day 6 to 18 of gestation aborted; at 35 mg/kg, a significant increase in skeletal malformations was recorded in the offspring.
- Concomitant use of dantrolene infusion

WARNINGS

Cardiac Conduction

Taro-Diltiazem T (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 CONTRAINDICATIONS).

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.

Hypotension

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

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.

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

ADVERSE REACTIONS). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

PRECAUTIONS

Impaired Hepatic or Renal Function

Because Taro-Diltiazem T (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 ADVERSE REACTIONS).

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.

Pediatric Use

Safety and effectiveness in children have not been established.

Nursing Mothers

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Taro-Diltiazem T 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.

Drug Interactions

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, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine,

propafenone, terfenadine, theophylline.

Table 1- 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.

Table 1- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
Beta-Blockers	T, CT	Arrhythmic effect ↑ propranolol exposure	The concomitant administration of diltiazem with beta-adrenergic blocking drugs warrants caution because of rhythm disturbances occurrence, and requires close medical supervision and ECG monitoring, particularly at the beginning of treatment. Such an association may have 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
Anti-H2 agents (Cimetidine, ranitidine)	CT	↑ cimetidine, ranitidine exposure	A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma Cmax 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.

Table 1- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
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)
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.

Table 1- Established or Potential Drug-Drug Interactions			
Agent	Ref	Effect	Clinical comment
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.
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 Cmax (3.6 -fold) and AUC (5-fold) of simvastatin were increased significantly.
Theophylline	T	↑ antihypertensive	Increased antihypertensive effects.

Other Calcium Antagonists: 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.

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 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.

ADVERSE REACTIONS

Overall Diltiazem Safety Profile

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%).

The following events were reported with a frequency of less than 1%:

Cardiovascular: 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 Hepatic WARNINGS).

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

The following postmarketing events have been reported infrequently in patients receiving diltiazem: sinoatrial block, congestive heart failure, acute generalized exanthematous pustulosis, alopecia, hyperglycemia, diabetes (new onset), worsening of existing diabetes (type 1 or type 2), angioedema, angioneurotic oedema, vasculitis, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, occasionally desquamative erythema with or without fever, gingival hyperplasia, gynecomastia, hemolytic anemia, hepatitis, increased bleeding time, leukopenia, mood changes (including depression), purpura, retinopathy, Stevens-Johnson syndrome thrombocytopenia, sweating, toxic epidermal necrolysis, photosensitivity (including lichenoid

keratosis at sun exposed skin areas). In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

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 percentage 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%), edema (3%), GI disease (2%), pain (5%), vasodilation (1%), asthenia (6%), dizziness (4%), palpitations (2%), pharyngitis (2%), rhinitis (2%), dyspnea (1%), nervousness (2%), paresthesia (2%), tachycardia (2%).

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

The following percentage 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%).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

Events observed following diltiazem overdose included bradycardia, hypotension, heart block 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.

DOSAGE AND ADMINISTRATION

Taro-Diltiazem T should not be chewed or crushed. Taro-Diltiazem T has not been shown to be bioequivalent to other diltiazem formulations, with the exception of TIAZAC (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and CLINICAL TRIALS).

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 Taro-Diltiazem T 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: 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.

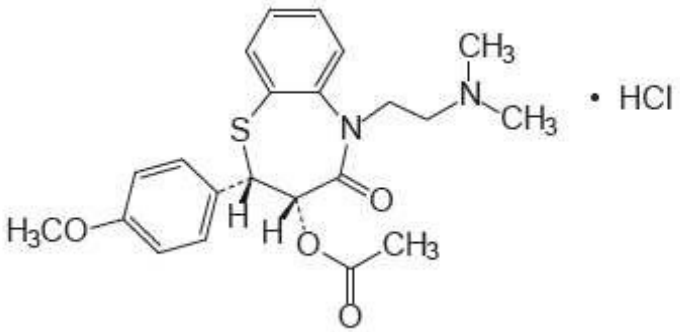
There is limited experience with doses above 360 mg. However, the incidence of adverse events increases as the dose increases with first degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose. Therefore, doses greater than 360 mg are not recommended.

PHARMACEUTICAL INFORMATION

Drug Substance

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

Chemical Structure



Empirical Formula $C_{22}H_{26}N_2O_4S \cdot HCl$

Molecular Weight 450.98

Description
Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform.

Composition
Taro-Diltiazem T extended-release capsules contain diltiazem hydrochloride and the following nonmedicinal ingredients: ethylcellulose, hypromellose, sugar spheres, talc, and triethyl citrate.

The gelatin capsules contain: FD&C blue#1, FD&C red #3 (120 mg, 240 mg, 300 mg strengths only), FD&C green#3 (180 mg, 240 mg and 360 mg strengths only), D&C yellow 10 (180 mg, 240 mg, and 360 mg strengths only), gelatin, sodium lauryl sulphate and titanium dioxide.

All capsules are imprinted with black ink which contains: ammonia solution, black iron oxide, potassium hydroxide, propylene glycol and shellac.

Storage Recommendations
Store at room temperature (15-30°C). Do not refrigerate. Protect from light and moisture.

AVAILABILITY OF DOSAGE FORM

Taro-Diltiazem T (Diltiazem Hydrochloride Extended-Release capsules USP) are available in the following strengths.

Taro-Diltiazem T 120 mg capsules are supplied in bottles of 90. Each purple colored cap and body capsule is imprinted, in black ink, with ”669” on cap and body.

Taro-Diltiazem T 180 mg capsules are supplied in bottles of 90. Each green colored cap and white colored body capsule is imprinted, in black ink, with ”670” on cap and body.

Taro-Diltiazem T 240 mg capsules are supplied in bottles of 90. Each purple colored cap and green colored body capsule is imprinted, in black ink, with "671" on cap and body.

Taro-Diltiazem T 300 mg capsules are supplied in bottles of 90. Each purple colored cap and white colored body capsule is imprinted, in black ink, with ”672” on cap and body.

Taro-Diltiazem T 360 mg capsules are supplied in bottles of 90. Each green colored cap and body capsule is imprinted, in black ink, with ”673” on cap and body.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Taro-Diltiazem T (Diltiazem Hydrochloride) 360 mg Extended Release capsules manufactured by Sun Pharmaceutical Industries Limited and ^{Pr}Tiazac® (Diltiazem Hydrochloride) 360 mg Extended Release capsules (Biovail Pharmaceuticals, Division of Biovail Corporation) in 33 healthy male subjects from 19 - 43 years of age, under fasting conditions was performed. The results from measured data are summarized in the following table.

Fasting Study
SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 360 mg) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/ml)	6911.20 7271.62 (31.8)	7064.48 7491.84 (34.0)	97.97	92.21 to 104.09
AUC_I (ng.h/ml)	7238.83 7649.73 (33.1)	7300.10 7749.90 (34.4)	99.32	93.56 to 105.44
C_{max} (ng/ml)	404.35 422.69 (29.8)	373.29 390.77 (30.8)	108.35	101.17 to 116.05
T_{max}§ (h)	5.77 (23.2)	6.97 (33.2)		
$T_{½}$§ (h)	9.27 (26.6)	8.10 (19.0)		

* Taro-Diltiazem T (Diltiazem Hydrochloride) 360 mg Extended Release capsules (Sun Pharmaceutical Industries Limited, Halol, India)
† ^{Pr}Tiazac® (Diltiazem Hydrochloride) 360 mg Extended Release capsules (Biovail Pharmaceuticals, Division of Biovail Corporation) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

A randomized, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Taro-Diltiazem T (Diltiazem Hydrochloride) 360 mg Extended Release capsules manufactured by Sun Pharmaceutical Industries Limited and ^{Pr}Tiazac® (Diltiazem Hydrochloride) 360 mg Extended Release capsules (Biovail Pharmaceuticals, Division of Biovail Corporation) in 30 healthy male subjects from 21 - 44 years of age, under fed conditions was performed. The results from measured data are summarized in the following table.

Fed Study
SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diltiazem (1 x 360 mg) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/ml)	6685.40 7142.10 (36.6)	6931.74 7307.56 (32.7)	96.45	90.21 to 103.11
AUC_I (ng.h/ml)	6841.21 7318.44 (37.1)	7072.73 7464.71 (33.1)	96.73	90.46 to 103.42
C_{max} (ng/ml)	478.76 500.38 (30.1)	507.52 534.04 (35.4)	94.33	88.06 to 101.06
T_{max}§ (h)	6.73 (28.5)	6.07 (9.4)		
$T_{½}$§ (h)	7.06 (23.1)	7.14 (19.0)		

* Taro-Diltiazem T (Diltiazem Hydrochloride) 360 mg Extended Release capsules (Sun Pharmaceutical Industries Limited, Halol, India)
† Pr Tiazac® (Diltiazem Hydrochloride) 360 mg Extended Release capsules (Biovail Pharmaceuticals, Division of Biovail Corporation) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

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 (100µ 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	187	(165-211)
	Rats	M&F	211	(155-287)
i.v.	Mice	M&F	58-61	(52-69)
	Rats	M&F	38-39	(34-44)

Toxic effects appeared rapidly and toxicity included reduction of spontaneous activity, ptosis, piloerection, ataxia, loss of muscle tone and loss of righting reflex. Gross autopsy of animals 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 istopathological 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-	80	Day 12 to 14	Brachydactyly, hematoma of the

peritoneal			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 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

[Pr]Taro-Diltiazem T

Diltiazem hydrochloride Extended-Release Capsules USP

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

Read this carefully before you start taking Taro-Diltiazem T and each time you get a refill. This leaflet is a summary and will not tell you everything about Taro-Diltiazem T. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about Taro-Diltiazem T.

ABOUT THIS MEDICATION

What the medication is used for:

Taro-Diltiazem T is used for:

- the treatment of mild to moderate **high blood pressure**.
- the management of effort associated **angina** (chest pain)

Taro-Diltiazem T 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:

Taro-Diltiazem T belongs to the group of drugs called "calcium channel blockers" or "calcium antagonists". Taro-Diltiazem T relaxes the arteries, thereby lowering blood pressure.
Taro-Diltiazem T reduces the amount of oxygen that your heart muscle needs. This helps control chest pain.

When it should not be used?

Do not use Taro-Diltiazem T if:

- You are pregnant or plan to become pregnant.
- You are breastfeeding.
- You have a known allergy to diltiazem or to any of the non-medicinal ingredients
- You have very low blood pressure (< 90 mmHg systolic).
- You have heart rhythm disorders in the absence of a pacemaker.
- You have severe heart failure with fluid in the lungs.
- You are taking a medicine called dantrolene used for severe muscle spasms or severe fever.

What the medicinal ingredient is:

Diltiazem Hydrochloride

What the nonmedicinal ingredients are:

Taro-Diltiazem T extended-release capsules contain the following nonmedicinal ingredients: ethylcellulose, hypromellose, sugar spheres, talc, and triethyl citrate.

The gelatin capsules contain: FD&C blue#1, FD&C red #3 (120 mg, 240 mg, 300 mg strengths only), FD&C green#3 (180 mg, 240 mg and 360 mg strengths only), D&C yellow 10 (180 mg, 240 mg, and 360 mg strengths only), gelatin, sodium lauryl sulphate and titanium dioxide.

All capsules are imprinted with black ink which contains: ammonia solution, black iron oxide, potassium hydroxide, propylene glycol and shellac.

What dosage forms it comes in:

Capsules: 120 mg, 180 mg, 240 mg, 300 mg and 360 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use Taro-Diltiazem T talk to your doctor or pharmacist if:

- You have a known allergy to diltiazem or any of the non-medicinal ingredients in Taro-Diltiazem T.
- You have very low blood pressure.
- You have ever had a bad or unusual reaction to any drug containing diltiazem in the past.
- You have heart, liver or kidney disease.
- You had a recent heart attack.
- You have high blood sugar or diabetes.
- You are 65 years or older.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, 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 Taro-Diltiazem T:
- Antifungal medications with a name ending in azole;
- Medications used to control the immune system such as cyclosporine;
- Certain antibiotics should not be taken with Taro-Diltiazem T such as erythromycin, rifampin. Check with your pharmacist if you are not sure;
- Sleeping pills such as benzodiazepines (midazolam, triazolam);
- Other blood pressure medications: alpha antagonists, beta-blockers;
- Heart medications: Amiodarone, digoxin, digitalis, flecainide, nifedipine, propafenone, quinidine, verapamil;
- 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 as anticoagulant;
- 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 Taro-Diltiazem T.
- Multivitamins with minerals (calcium-containing products).
- Drugs to treat inflammation: Corticosteroids, methylprednisolone.
- Dantrolene used for severe muscle spasms or severe fever.

Alcohol may cause low blood pressure and dizziness 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 when consumed too often while taking Taro-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 grapefruit juice be avoided if this happens to you.

PROPER USE OF THIS MEDICATION

-Do not miss doses or take extra doses, unless your doctor tells you. If you are not clear about the directions, ask your doctor or pharmacist.

Take Taro-Diltiazem T exactly as your doctor tells you. Taro-Diltiazem T is taken once a day at about the same time every day.
DO NOT chew or crush Taro-Diltiazem T capsules.

Usual Adult Dose:
High blood pressure
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.

Angina
Dosage should be individualised
Starting dose: 120 mg to 180 mg once a day. Dose may be slowly (over 7 to 14 days) increased up to 360 mg a day. Always follow your doctor's instructions.

Overdose:

In case of drug overdose, contact a health care practitioner, 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;

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.	✓		
	Fast, slow, or irregular heartbeat		✓	
	Peripheral edema: swelling of the ankles	✓		
	Respiratory tract infection: pharyngitis, rhinitis		✓	
	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.	✓		

- Unusual tiredness and weakness;
- Upset stomach.

Taro-Diltiazem T can cause abnormal blood test results. Your doctor 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

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	
	Heart block: A disease in the electrical system of the heart causing lightheadedness, fainting and irregular heartbeat			✓
	Heart Attack: shortness of breath, chest pain			✓
	Angina: Chest pain		✓	
	Heart Failure: shortness of breath, leg swelling, and exercise intolerance.		✓	
	Eye Problems: decreased vision, irritation, sore red eyes	✓		
	Increased blood sugar: frequent urination, thirst, and hunger	✓		

Rare	**Liver Disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	

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**	
Unknown	**Serious Skin Reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Hypersensi-tivity 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 Taro-Diltiazem T, contact your doctor or pharmacist.

HOW TO STORE IT

Store Taro-Diltiazem T capsules at room temperature (15-30°C). Avoid excessive humidity.
Keep out of sight and reach of children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.taro.ca

or by contacting the sponsor,
Taro Pharmaceuticals Inc., at: **1-800-268-1975**

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