PRODUCT MONOGRAPH

[Pr]pms-DIGOXIN®

Digoxin Tablets, C.S.D. 0.0625 mg, 0.125 mg and 0.25 mg

Cardiotonic Glycoside

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets: 0.0625 mg, 0.125 mg and 0.25 mg	Tablets: Lactose (hydrous), Corn Starch, Pregelatinized Starch, Magnesium Stearate D&C Yellow #10, FC&C Yellow #6

INDICATIONS AND CLINICAL USE

PMS-DIGOXIN® (Digoxin Tablets, C.S.D.) is indicated for:

Congestive Heart Failure: PMS-DIGOXIN is indicated for the treatment of mild to moderate heart failure. PMS-DIGOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, PMS-DIGOXIN should be used with a diuretic and angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

Digoxin is usually continued after failure is controlled unless some known precipitating factor is corrected. Studies have shown that withdrawal of digoxin may worsen functional status, exercise capacity, and the left ventricular ejection fraction in patients with heart failure. In patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

Atrial Fibrillation: PMS-DIGOXIN is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

Geriatrics (> 70 years of age):

Although appropriate studies on the relationship of age to the effects of digitalis glycosides have not been performed in the geriatric population, the majority of experience with digoxin is in this population. This drug is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients may be more likely to have age-related renal function impairment, which may significantly increase the elimination half-life of digoxin, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (See Dosage and Administration).

Pediatrics (< 10 years of age):

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effect of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalization in infants and children must be individualized (See Dosage and Administration).

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to PMS-DIGOXIN® (Digoxin Tablets, C.S.D.). Hypersensitivity to PMS-DIGOXIN® itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS AND PRECAUTIONS

General

Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of the symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of Digoxin Tablets, C.S.D. (see Dosage and Administration).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin Tablets, C.S.D.should be discontinued as soon as possible, especially if a therapeutic trial does not result in improvement. Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive and dosage must not only be reduced but must be individualized according to their degree of maturity. Impaired renal function must also be carefully taken into consideration.

Dosage of digoxin must be carefully titrated and differences in the bioavailability of parenteral preparations, oral solution and tablets taken into account when changing patients from one preparation to another.

Carcinogenesis and Mutagenesis

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

Cardiovascular

Use During Electrical Cardioversion:
Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Sinus Node Disease and AV Block:
Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate. If digitalization is essential, electrical pacing of the ventricles may be indicated. In some patients with sinus node disease (i.e., Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sinoatrial block. Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Accessory AV Pathway (Wolff-Parkinson-White Syndrome):

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Use in Patients with preserved Left Ventricular Systolic Function:
Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed. Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output. Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin. Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Use in Patients with Acute Myocardial Infarction:
Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

Dependence/Tolerance

No drug dependence has been reported with the use of digoxin.

Endocrine and Metabolism

In Patients with Electrolyte Disorders:
In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the normal range, because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from peritoneal or hemodialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, long-standing heart failure, long-standing wasting diseases and treatment with ion-exchange resins or carbenoxolone. In general, rapid changes in serum potassium or other electrolytes should be avoided, and i.v. treatment with potassium should be reserved for special circumstances as described below (see Overdose: Symptoms and Treatment).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus digoxin may be ineffective until serum calcium is restored to normal. These interactions are elated to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Use in Thyroid Disorders and Hypermetabolic States:
In hypothyroidism the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

Renal
In Patients with Renal Disease:
Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see Dosage and Administration).

If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous 2 weeks, the dose of digoxin must be reduced accordingly. Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see Dosage and Administration). Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

Special Populations

Pregnant Women:
Teratogenic Effects: Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, although there have been no reports of teratogenic effects following the use of digoxin in pregnancy since its availability in 1929. Digoxin should be given to pregnant women only if clearly needed.

Nursing Women:
Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

Pediatrics (< *10* years of age):
Digitalis glycosides are a major cause of poisoning in children. The tolerance of newborn infants to digitalis glycosides is variable, since their renal clearance of the medication is reduced. Premature and immature infants are especially sensitive. Dosage of digoxin should be reduced and individualized according to the infant's degree of maturity, since renal clearance increases as the infant matures. Children older than 1 month of age generally require proportionally larger doses than adults on the basis of body weight or body surface area.

Geriatrics (> 70 years of age):
Although appropriate studies on the relationship of age to the effects of digitalis glycosides have not been performed in the geriatric population, the majority of experience with digoxin is in this population. Elderly patients may be more likely to have age-related renal function impairment, which may significantly increase the elimination half-life of digoxin. Additionally, elderly patients may have a decreased volume of distribution of digitalis due to decreased muscle mass. These factors may contribute to digitalis toxicity in elderly patients.

Monitoring and Laboratory Tests

Patients receiving Digoxin Tablets, C.S.D. should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see Dosage and Administration.

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.
Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half', gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in-recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking digoxin compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

Clinical Trial Adverse Drug Reactions

Adults:

Cardiac:
Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Persistent bigeminy at rest but not on exercise when the sinus rate increases has traditionally been acceptable in the management of some arrhythmias. Ventricular tachycardia and ventricular fibrillation may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage. Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block (including asystole).

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

Digoxin may also induce other changes in the ECG (e.g., PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (See Warnings and Precautions).

Gastrointestinal:
Anorexia, nausea, vomiting, and less commonly, diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Rarely, the use of digoxin has been associated with abdominal pain.

It is inadvisable to rely on nausea as an early warning of excessive digoxin as arrhythmias may occur first.

Central Nervous System:
Visual disturbances (blurred or yellow vision), headache, weakness, apathy, psychosis, and mental disturbances (such as anxiety, depression, delerium, and hallucination) can occur.

Other:
Gynecomastia is occasionally observed following prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

Table 1 summarizes the incidence of those adverse experiences listed above for patients treated with digoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in Table 1 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with

results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

TABLE 1: Adverse Experiences in Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials with digoxin tablets (Number of Patients Reporting)		
Adverse Experience	**Digoxin Patients (n=123) (%)**	**Placebo Patients (n=125) (%)**
Cardiac		
Palpitation	1 (0.8)	4 (3.2)
Ventricular extrasystole	1 (0.8)	1 (0.8)
Tachycardia	2 (1.6)	1 (0.8)
Heart arrest	1 (0.8)	1 (0.8)
Gastrointestinal		
Anorexia	1 (0.8)	4 (3.2)
Nausea	4 (3.3)	2 (1.6)
Vomiting	2 (1.6)	1 (0.8)
Diarrhea	4 (3.3)	1 (0.8)
Abdominal pain	0	6 (4.8)
CNS		
Headache	4 (3.3)	4 (3.2)
Dizziness	6 (4.9)	5 (4.0)
Mental disturbances	5 (4.1)	1 (0.8)
Other		
Rash	2 (1.6)	1 (0.8)
Death	4 (3.3)	3 (2.4)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Gastrointestinal: Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

Other: Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

Infants and Children:

Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication, until further evaluation proves otherwise.

Post-Market Adverse Drug Reactions

Adverse reactions to digoxin are usually dose dependent and occur at dosages higher than those needed to achieve a therapeutic effect.

DRUG INTERACTIONS

Overview

Digitalis glycosides have a narrow therapeutic range and changes in digoxin pharmacokinetics and/or pharmacodynamics caused by a digoxin-drug interaction can result in toxicity or underdigitalization. The presence of or a change in an underlying disease state also can cause changes in digoxin pharmacokinetics and/or pharmacodynamics and may complicate or contribute to a digoxin-drug interaction. Because a risk of digoxin toxicity exists, and the clinical significance of an interaction may be variable and not necessarily predictable, it is important that the addition or withdrawal of a drug to or from a therapeutic regimen that includes digoxin be carefully evaluated in the context of the patient and the clinical situation.

Potassium-depleting corticosteroids and diuretics may be major contributing factors to digitalis toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose.

Certain antibiotics [Erythromycin and clarithromycin (and possibly other macrolide antibiotics) and tetracycline] may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentrations relates to the extent of bacterial inactivation, and may be as much as 2 fold in some cases.

Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestryramine, phenytoin, St. John's wort (Hypericum perforatum) and certain anticancer drugs may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. Thyroid administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. Succinylcholine may cause a sudden extrusion of potassium from muscle cells and may thereby cause arrhythmias in digitalized patients. Although α-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in

renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

Drug-Drug Interaction

Table 2: Established or Potential Drug-Drug Interactions with Digoxin

Interacting Drugs	Ref	Effect	Clinical comment
Albuterol	USP DI 2004	Concurrent use may decrease serum digoxin concentrations, possibly by redistributing digoxin to other tissues. Albuterol may also decrease serum potassium concentrations, which may increase the risk of digoxin toxicity.	
Alprazolam	USP DI 2004	Concurrent use may increase serum digoxin concentrations, possibly by decreasing the renal clearance of digoxin; although one small study performed in healthy volunteers concluded that alprazolam had no significant effect on digoxin clearance, contradictory evidence has been reported in patients [primarily elderly patients] receiving long-term digoxin therapy.	
Amiodarone	USP DI 2004	Increases in serum digoxin concentrations by as much as 100% have been reported with concurrent use. Although it is thought that amiodarone decreases renal and/or nonrenal clearance and/or the volume of distribution of digoxin, other contributing factors, such as amiodarone-induced displacement of digoxin from tissue binding sites, also may be involved. Amiodarone has a long elimination half-life [15 to 65 days or longer] and digoxin toxicity may not appear until several weeks after the addition of amiodarone or may persist long after discontinuation of amiodarone	
Antacids or Antidiarrheal adsorbents (e.g., kaolin and pectin) or Sulfasalazine	USP DI 2004	Concurrent use may decrease digoxin bioavailability by decreasing digoxin absorption.	In the case of antidiarrheal adsorbents and sulfasalazine, the digoxin dose may be administered 8 hours before the interacting medication.
Antibiotics, oral, especially Macrolide antibiotics, such as: Clarithromycinor Erythromycin or Tetracycline	USP DI 2004	Concurrent use of some oral antibiotics may increase serum digoxin concentrations in patients who inactivate digoxin in the lower intestine by bacterial metabolism; in these individuals, altering the bowel flora with certain antibiotics may diminish digoxin conversion to inactive metabolites, resulting in increased serum digoxin concentration; the increase in serum digoxin concentration has been as much as twofold in some cases and correlates with the extent of bacterial inactivation. Although there are limited data, this interaction has been reported with oral use of clarithromycin, erythromycin, and tetracycline	

Anticancer medications (such as bleomycin, cyclophosphamide, cytarabine, doxorubicin, procarbazine, and vincristine) or Radiation therapy	USP DI 2004	Concurrent use may decrease digoxin bioavailability by decreasing digoxin absorption; the reduced absorption that occurs during concurrent use with anticancer medications or radiation therapy may be due to temporary damage to the gastrointestinal mucosa and may continue for several days after treatment. However, digitoxin absorption does not appear to be affected by anticancer agents.	In the case of concurrent use of anticancer medications, a dosage form with greater bioavailability, such as the capsule or solution, may help to minimize decreased bioavailability.
Atorvastatin	USP DI 2004	Concurrent use may increase digoxin serum concentrations; steady-state serum concentration increases of approximately 20% have been reported.	
Beta-adrenergic blocking agents including Atenolol, Carvedilol, Metoprolol and Propranolol	USP DI 2004	Concurrent use with these agents may have additive effects on slowing atrioventricular [AV] nodal conduction; concurrent use with carvedilol in patients with hypertension increased the steady-state area under the plasma concentration–time curve [AUC] and trough concentrations of digoxin by 14% and 16%, respectively.	Plasma digoxin concentrations should be monitored when digoxin is co-administered with beta-adrenergic blocking agents.
Bran fiber, dietary	USP DI 2004	It is uncertain whether concurrent administration of dietary bran fiber decreases digoxin bioavailability. In one small study, there was presumed to be a decrease in digoxin absorption when concurrent administration of digoxin with 5 grams of fiber resulted in a decrease in urinary excretion of digoxin. Another small study found no change in steady-state serum digoxin concentrations when digoxin was administered 15 to 30 minutes before administration of 11 grams of bran [as a bran muffin], with a second bran muffin administered several hours later.	

Calcium channel blocking agents, especially Bepridil or Diltiazem or Nifedipine or Verapamil	USP DI 2004	Concurrent use with calcium channel blocking agents may have additive effects on AV nodal conduction, which could result in complete heart block; concurrent use also may increase serum digoxin concentrations by reducing digoxin renal clearance, possibly as a result of inhibition of active tubular secretion of digoxin; verapamil may increase serum digoxin concentrations by 30 to 200%; bepridil may increase serum digoxin concentrations by approximately 34%; some studies have reported no interaction with diltiazem while others have reported increases in serum digoxin concentrations of 20 to 60%; contradictory evidence of an interaction also exists for nifedipine, although serum digoxin increases of 15 to 50% have been reported; increases in serum digitoxin concentrations also have been reported with concurrent use of diltiazem and verapamil, although increases were less pronounced than with digoxin use and may be due to a reduction in extrarenal digitoxin clearance.	Serum digitalis concentrations and electrocardiogram [ECG] should be monitored and dosages should be adjusted accordingly.
Cholestyramine or Colestipol	USP DI 2004	Colestipol and cholestyramine may delay and reduce the absorption of digoxin.	Digoxin dose may be administered 8 hours before the interacting medication to minimize the interference with digoxin absorption.

Interacting Drugs	**Ref**	**Effect**	**Clinical comment**
Cyclosporine	USP DI 2004	Concurrent use has resulted in increases in serum digoxin concentrations, possibly as a result of decreased apparent volume of distribution and/or plasma clearance of digoxin.	
Diphenoxylate or Propantheline	USP DI 2004	Concurrent use may increase digoxin bioavailability; diphenoxylate and propantheline increase digoxin absorption by decreasing intestinal motility.	
Diuretics, potassium-depleting (such as bumetanide, ethacrynic acid, furosemide, indapamide, mannitol, or thiazides) or Hypokalemia-causing medications	USP DI 2004	Decreases in serum potassium concentrations that can occur with these medications may increase the risk of digitalis toxicity.	Frequent serum potassium concentration determinations are recommended when these medications are concurrently administered with digoxin.

Flecainide	USP DI 2004	Concurrent use has increased serum digoxin concentrations, on average, by 24%; it also has been speculated that concurrent use may cause a slight additive increase in the PR interval	
Hepatic enzyme inducers, such as: Barbiturates or Phenytoin or Rifampin	USP DI 2004	Concurrent use may increase the metabolism of digitoxin; serum digitoxin concentrations have been reported to decrease by 50% in patients who received 180 mg of phenobarbital per day for 12 weeks; decreases in serum digoxin concentrations also have been reported with concurrent use of rifampin, although the mechanism for this interaction is not completely understood.	Serum digitalis concentrations should be monitored and dosages adjusted accordingly.
Indomethacin	USP DI 2004	Concurrent use may increase digoxin serum concentrations, possibly by inhibiting the renal elimination of digoxin; two small studies that evaluated the interaction in healthy adult patients did not find a clinically significant interaction. Another small study found a significant increase [about 40% on average] in serum digoxin concentrations in adult heart failure patients treated with digoxin on a long-term basis. A small study in premature infants treated conventionally with indomethacin for patent ductus arteriosus [PDA] found an increase in serum digoxin concentrations of approximately 50% with concurrent use.	
Itraconazol	USP DI 2004	Concurrent use may increase serum digoxin concentrations, possibly by decreasing renal elimination of digoxin; serum digoxin concentration increases of approximately 50% have been reported	
Metoclopramide	USP DI 2004	Concurrent use of metoclopramide may decrease digoxin absorption by increasing gastrointestinal motility; serum digoxin concentrations as determined by AUC have been reported to decrease by about 24%.	
Neomycin, oral	USP DI 2004	Concurrent use decreases the rate and extent of absorption of digoxin. In a study in healthy volunteers, the extent of absorption of digoxin was decreased by as much as 51% after single doses of digoxin and neomycin. The absorption of digoxin also was decreased when the antibiotic was given 3 or 6 hours before the digoxin dose. The mechanism of this interaction has not been established.	It is recommended that digoxin be administered at least 8 hours before neomycin
Omeprazole	USP DI 2004	Concurrent use with digoxin may increase digoxin absorption, possibly by altering gastric acidity; on average, C_{max} and AUC values have been reported to be about 10% higher with concurrent use.	

Propafenone	USP DI 2004	Concurrent use of propafenone with digoxin results in an increase in serum digoxin concentrations ranging from 35 to 85%, which appears to be unrelated to digoxin renal clearance but may be related to a decrease in the volume of distribution and nonrenal clearance of digoxin.	Careful monitoring of digoxin concentrations and dosage reduction of digoxin are recommended when propafenone is initiated,
Quinidine or Quinine	USP DI 2004	Concurrent use with quinidine has resulted in increased digoxin plasma concentrations, possibly due to an initial displacement of digoxin from quinidine binding sites, and a reduction in the renal and nonrenal clearance and volume of distribution of digoxin; the extent of the interaction is proportional to plasma quinidine concentrations and, on average, concurrent use results in 100% increases in serum digoxin concentrations, although increases of over 300% have been reported; concurrent use of quinidine with digitoxin has resulted in increases in serum digitoxin concentrations of 30 to 67%, the smaller increases possibly resulting from impairment of extrarenal clearance of digitoxin by quinidine; increases in serum digoxin concentrations also have been reported with concurrent use of quinine.	Serum digitalis concentrations should be monitored and dosage adjusted as indicated.
Spironolactone	USP DI 2004	Concurrent use with digoxin may increase serum digoxin concentrations, possibly by decreasing digoxin renal and nonrenal clearance and/or digoxin volume of distribution; it has been estimated that digoxin plasma concentrations may increase by one third with concurrent use	
Succinylcholine	USP DI 2004	Concurrent use may cause a sudden release of potassium from muscle cells, increasing the risk of arrhythmias in digitalized patients	
Sucralfate	USP DI 2004	Sucralfate was reported to reduce digoxin plasma concentrations by about 19%, presumably by reducing the bioavailability of digoxin.	Sucralfate should not be taken within 2 hours of digoxin
Sympathomimetics	USP DI 2004	Concurrent use may increase the risk of cardiac arrhythmias.	
Thyroid hormones	USP DI 2004	Patients with thyroid disease may have an altered sensitivity to digitalis: hyperthyroid patients may have a reduced response to digitalis and hypothyroid patients may have an increased risk of digitalis toxicity.	Increase in digitalis dose may be required with the use of thyroid hormones in a hypothyroid patient.

Drug-Herb Interactions

St. John's wort (Hypericum perforatum) may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. Patients are advised to consult with their doctors before taking herbal products.

Drug-Laboratory Interactions

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

Drug-Lifestyle Interactions

Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

DOSAGE AND ADMINISTRATION

General: Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.
In selecting the dose of digoxin, several factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon (i.e., ideal) body weight.
2. The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (i.e., below 1.5 mg/dL).
4. Concomitant disease states, concurrent medication or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see Precautions).
5. To minimize toxic side effects, the lowest effective dose should be used as the maintenance dose.

Serum Digoxin Concentrations:

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of

adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/mL. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/mL, values below 2.0 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:
1. Analytical problems in the assay procedure.
2. Inappropriate serum sampling time.
3. Administration of a digitalis glycoside other man digoxin.
4. Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.
5. Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

Heart Failure:

Adults: Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1- Rapid digitalization may be achieved by administering a loading dose based upon projected peak body digoxin stores, then calculating the maintenance dose as a percentage of the loading dose.
2- More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 5 half-lives of the drug for the individual patient. Depending upon the patient’s renal function, this will take between 1 and 3 weeks.

Rapid Digitalization with a Loading Dose: Peak body digoxin stores of 8 to 12 µg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 µg/kg) [see PRECAUTIONS].

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, **with careful assessment of clinical response before each additional dose**.

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

A single initial dose of 500 to 750 µg (0.5 to 0.75 mg) of PMS-DIGOXIN Tablets usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 125 to 375 µg (0.125 to 0.375 mg) may be given cautiously at 6 to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of PMS-DIGOXIN Tablets that a 70-kg patient requires to achieve 8 to 12 µg/kg peak body stores is 750 to 1250 µg (0.75 to 1.25 mg).

Digoxin injection is frequently used to achieve rapid digitalization, with conversion to Digoxin Tablets for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see Table 1, ACTION AND CLINICAL PHARMACOLOGY).

Maintenance Dosing:

The doses of digoxin used in controlled trials in patients with heart failure have ranged from 125 to 500 µg (0.125 to 0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 µg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 µg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 µg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.

In a subset of approximately 1,800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in Table 5) the mean (± SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/mL and 0.97 ± 0.43 ng/mL, respectively.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:

$$\text{Maintenance dose} = \text{Peak body stores (i.e., Loading Dose)} \times \frac{\%\ \text{Daily Loss}}{100}$$

Where % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area.)

Table 3: Usual Daily Maintenance Dose Requirements of Digoxin (μg) for Estimated Peak Body Stores of 10 μg/kg

	Lean Body Weight							Number of Days Before Steady State Achieved**
Corrected Ccr	kg	50	60	70	80	90	100	
(mL/min per 70 kg)*	lb	110	132	154	176	198	220	
0		62.5***	125	125	125	187.5	187.5	22
10		125	125	125	187.5	187.5	187.5	19
20		125	125	187.5	187.5	187.5	250	16
30		125	187.5	187.5	187.5	250	250	14
40		125	187.5	187.5	250	250	250	13
50		187.5	187.5	250	250	250	250	12
60		187.5	187.5	250	250	250	375	11
70		187.5	250	250	250	250	375	10
80		187.5	250	250	250	375	375	9
90		187.5	250	250	250	375	500	8
100		250	250	250	375	375	500	7

*Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. For adults, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 - Age)/Scr. For women, this result should be multiplied by 0.85. *Note*: This equation cannot be used for estimating creatinine clearance in infants or children.
** If no loading dose administered.
*** 62.5 mcg = 0.0625 mg

Example: Based on Table 3, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 mL/min, should be given 250 µg (0.25 mg) daily of PMS-DIGOXIN Tablet, usually taken after the morning meal. If no loading dose is administered, steady-state serum concentration in this patient should be anticipated at approximately 11 days.

Infants and Children:
In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Daily maintenance doses for each age group are given in Table 4 and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function:

Table 4: Daily Maintenance Doses of PMS-DIGOXIN Tablets in Children with Normal Renal Function

Age	Daily Maintenance Dose (µg/kg)
2 to 5 years	10 to 15
5 to 10 years	7 to 10
Over 10 years	3 to 5

Gradual Digitalization with a Maintenance Dose
More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in Table 4 can be used in calculating this dose for patients with normal renal function.

It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

Atrial Fibrillation:

Adults and Children: Peak digoxin body stores larger than the 8 to 12 µg /kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

Dosage Adjustment When Changing Preparations: The difference in bioavailability between intravenous digoxin and PMS-DIGOXIN Tablets must be considered when changing patients from one dosage form to another.

It has been shown that differences in formulations of digoxin, despite an identical content of active ingredient, may be associated with differences in fractional gastrointestinal absorption. Consequently, differences in bioavailability between PMS-DIGOXIN Tablets and other brands of digoxin tablets must be considered when changing from one brand to another. In switching to another digoxin product, particular emphasis needs to be placed on clinical monitoring of patients and monitoring of serum digoxin levels and potassium levels. Small changes in serum levels of digoxin may lead to inadequate digitalization or to toxicity. Inadequate digitalization may result in the reappearance of symptoms of atrial fibrillation such as tachycardia, palpitations and dyspnea. Toxic levels of digoxin may produce loss of appetite, nausea and vomiting, drowsiness, bradycardia, and visual disturbances. These effects are particularly important in elderly and

pediatric patients and in those with co-existing diseases or receiving concurrent medication. It is therefore important that prescribers, pharmacists and patients be aware that substitiution of PMS-DIGOXIN Tablets with any other oral formulation of digoxin is not recommended as this may lead to alterations in digoxin serum levels. For this reason, it may be appropriate to prescribe by brand.

Missed Dose

If a dose is missed patients are advised to take the dose as soon as remembered if within 12 hours of scheduled dose and not taking if remembered later. Patients are advised not to double doses and to consult their doctor if a dose is missed for 2 days or more.

Administration
Digoxin is usually administered orally as a single daily dose. Divided daily dosing is recommended in infants and young children.

OVERDOSAGE

Adults:
Digoxin should be temporarily discontinued until the adverse reaction resolves.

Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances or concurrent medications). Once the adverse reaction has resolved, therapy with digoxin may be reinstituted, following a careful reassessment of dose.

Withdrawal of digoxin may be all that is required to treat the adverse reaction. However, when the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed.

If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration should be given to the reversal of toxicity with DIGIBIND® [Digoxin Immune Fab (Ovine)] (see Massive Digitalis Overdosage subsection), the use of atropine, or the insertion of a temporary cardiac pacemaker. However, asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac monitoring of the patient.
If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see Administration of Potassium subsection) or hypomagnesemia is present. DIGIBIND is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

Administration of Potassium
Every effort should be made to maintain the serum potassium concentration between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium maybe administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia.

Potassium salts may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection).

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include severe ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias or heart block. The administration of more than 10 mg of digoxin in a previously healthy adults, or more than 4 mg in a previously healthy child or a steady-state serum concentration greater than 10 ng/mL, often results in cardiac arrest.

DIGIBIND should be used to reverse the toxic effect of a massive overdose. The decision to administer DIGIBIND to a patient who has ingested a massive dose of digoxin but who has not yet manifested life-threatening toxicity should depend on the likelihood that the life-threatening toxicity will occur (see above).

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of potassium from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the setting of massive intoxication may be hazardous and should be avoided. Hyperkalemia caused by massive digitalis toxicity is best treated with DIGIBIND; initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The influence of digitalis glycosides on the myocardium is dose related, and involves both direct action on cardiac muscle and the specialized conduction system, and indirect actions on cardiovascular system mediated by the autonomic nervous system. The indirect actions mediated by the autonomic nervous system involve a vagomimetic action, which is responsible for the effects of digitalis on the sinoatrial (SA) and atrioventricular (AV) nodes; and also a baroreceptor sensitization which results in increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); a slowing of heart rate (negative chronotropic effect); and decreased conduction velocity through the AV node. In higher doses, digitalis increases sympathetic outflow from the CNS to both cardiac and peripheral sympathetic nerves. This

increase in sympathetic activity may be an important factor in digitalis cardiac toxicity. Most of the extracardiac manifestations of digitalis toxicity are also mediated by the CNS.

Pharmacodynamics

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.
The times to onset of pharmacologic effect and to peak effect of preparations of digoxin are shown in Table 6.

Table 6: Time to Onset of Effect and Peak Effect for Digoxin Products

Product	Time to Onset of Effect*	Time to peak Effect*
Digoxin Tablets, C.S.D.	0.5 to 2 hours	2 to 6 hours

* Documented for ventricular response rate in atrial fibrillation, ionotropic effect and electrocardiograph changes

Congestive Heart Failure:

Two 12-week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) patients with NYHA class II or III heart failure previously treated with digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with digoxin. Both trials demonstrated better preservation of exercise capacity in patients randomized to digoxin. Continued treatment with digoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction $\leq$ 0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or digoxin, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91 to 1.07). Digoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of digoxin was associated with a trend to increase time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in Table 7. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure. In situations where there is no statistically significant benefit of treatment evident from a trial's primary end point, results pertaining to secondary endpoint should be interpreted cautiously.

Table 7: Subgroup Analyses of Mortality and Hospitalization During the First Two Years Following Randomization in the DIG Trial with Digoxin

		Risk of All-Cause Mortality or All-Cause Hospitalization*			Risk of HF-Related Mortality or HF-Related Hospitalization*		
	n	Placebo	Digoxin	Relative risk†	Placebo	Digoxin	Relative risk†
All patients (EF □0.45)	6801	604	593	0.94 (0.88-1.00)	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)	244	190	0.74 (0.66-0.84)
CTR □0.55	4455	561	563	0.98 (0.91-1.06)	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)	402	295	0.65 (0.57-0.75)
EF <0.25	2258	677	637	0.84 (0.76-0.93)	394	270	0.61 (0.53-0.71)
CTR >0.55	2346	687	650	0.85 (0.77-0.94)	398	287	0.65 (0.57-0.75)
EF >0.45‡	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

Chronic Atrial Fibrillation:
In patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25 to 0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

Pharmacokinetics

Absorption:
Gastrointestinal absorption of digoxin is a passive process. Absorption of digoxin from tablets is 60 to 80%. Absorption of Digoxin Oral Solution formulation has been demonstrated to be 70% to 85% complete compared to an identical intravenous dose of digoxin (absolute bioavailability). When digoxin oral solution/tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fibre; however, the amount absorbed from an oral dose may be reduced.

In some patients, orally administered digoxin is converted to cardioinactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggest that 1 in 10 patients treated with digoxin tablets will degrade 40% or more of the ingested dose. As a result, certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these

bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate constant with the extent of bacterial interaction and may be as much as two-fold in some cases.

Distribution:
Following drug administration, a 6- to 8-hour distribution phase is observed. This is followed by a much more gradual serum concentration decline, which is dependent on digoxin elimination from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state postdistribution serum levels are in equilibrium with tissue levels and correlate with pharmacologic effects. In individual patients, these postdistribution serum concentrations are linearly related to maintenance dosage and may be useful in evaluating therapeutic and toxic effects.

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, serum digoxin concentration in the newborn is similar to the serum level in the mother. Approximately 20 to 25% of plasma digoxin is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (ideal) body weight, not total body weight.

Metabolism:

Metabolism occurs partially in the stomach, but also may occur in the liver and, although only about 16% of a dose of digoxin is metablolized, several metabolites of dogoxin and their metabolic pathways have been identified. The bis-digitoxoside and mono-digitoxoside metabolites are considered to be cardioactive. Other metabolites, such as digoxigenin, are considered to be less cardioactive than digoxin. In some patients (estimated to be approximately 10% of patients taking digoxin), other cardioinactive metabolites, such as dihydrodigoxin and dihydrodigoxigenin, may result from the metabolism of digoxin by intestinal bacteria. In these individuals, as much as 40% or more of the oral dose of digoxin may be converted to these inactive reduction products. The metabolism of digoxin is not dependent upon the cytochrome P-450 system.

Excretion:

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following i.v. administration to normal subjects, 50 to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2 days.

Special Populations and Conditions

Pediatrics:

The tolerance of newborn infants to digitalis glycosides is variable, since their renal clearance of the medication is reduced. Premature and immature infants are especially sensitive. Dosage should be reduced and individualized according to the infant's degree of maturity, since renal clearance increases as the infant matures. Children older than l month of age generally require proportionally larger doses than adults on the basis of body weight or body surface area (See Dosage and Administration).

Geriatrics:

Elderly patients may be more likely to have age-related renal function impairment, which may significantly increase the elimination half-life of digoxin. Additionally, elderly patients may have a decreased volume of distribution of digitalis due to decreased muscle mass. These factors may contribute to digitalis toxicity in elderly patients.

Gender:

Digoxin is primarily removed from the body by renal elimination. Although the digoxin clearance in women is about 10-15% lower than in men, the effect of gender on the pharmacokinetics of digoxin is not expected to be clinically significant when initiating and monitoring digoxin therapy in patients.

Race:

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

Hepatic Insufficiency:

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

Renal Insufficiency:

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. In children with renal disease, digoxin must be carefully titrated based on clinical response.

The half-life of digoxin in anuric patients is prolonged to 4 to 6 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion or during cardiopulmonary bypass because most of the drug is in the tissue rather than circulating in the blood.

Genetic Polymorphism:

The effect of genetic polymorphism on the pharmacokinetics of digoxin was not studied.

STORAGE AND STABILITY

Store between 15 to 30°C in a dry place and protect from light. Avoid exposure to excessive heat.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets:

0.0625 mg: Each round, peach, flat-faced, bevelled-edge tablet with code PMS-DIGOXIN U3A, contains: digoxin 0.0625 mg (62.5 µg). Nonmedicinal ingredients, FD&C Yellow No. 6, lactose, magnesium stearate, pregelatinized starch and starch (corn). Tartrazine-free. Bottles of 250.

0.125mg: Each round, yellow, flat-faced tablet, with code PMS-DIGOXIN Y3B on the same side as score mark, contains: digoxin 0.125 mg (125 µg). Nonmedicinal ingredients: FD&C Yellow No. 6, D&C Yellow No. 10, lactose, magnesium stearate, pregelatinized starch and starch (corn). Tartrazine-free. Bottles of 250 and 1000.

0.25 mg: Each round, white, biconvex tablet, with code PMS-DIGOXIN X3A on same side as score mark, contains: digoxin 0.25 mg (250 µg). Nonmedicinal ingredients: lactose,magnesium stearate, pregelatinized starch and starch (corn). Dye- and tartrazine-free. Bottles of 250 and 1000.

Product Monograph available upon request.

Pharmascience Inc.
Montréal, Québec H4P 2T4

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

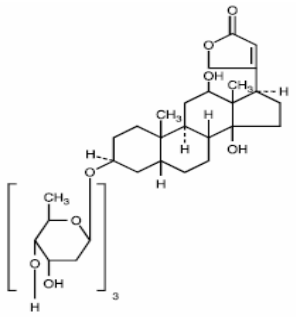
Drug Substance

Proper Name: Digoxin

Chemical Name: 3β-[(O-2, 6-dideoxy-β-D-*ribo*-hexopyranosyl-(1-4)-O-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1-4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide

Molecular formula and molecular mass: $C_{41}H_{64}O_{14}$; MW=780.95

Structural formula:
[USAN]



Physicochemical properties: Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

CLINICAL TRIALS

Study demographics and trial design

CLINICAL TRIALS

Study demographics and trial design

Table 8 - Summary of patient demographics for Controlled Clinical Trials for Digoxin in Congestive Heart Failure

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Digitalis Investigation Group (DIG Trial)	Randomized, double-blind, placebo-controlled	Daily dose: 0.125 - 0.500 mg tablets (median dose 0.25mg) Study duration: Range from 28 to 58 months (mean duration 37 months)	Total: 7,788 patients At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Main trial: (left ventricular ejection fractions of 0.45 or less): Digoxin- 3397 patients Placebo- 3403 patients Ancillary trial: (left ventricular ejection fractions greater than 0.45): Digoxin- 492 patients Placebo- 496 patients	Digoxin Mean age: 63.4 Range: 63.4 ± 11.0 Placebo Mean age: 63.5 Range: 63.5 ± 10.8	Digoxin Males and Females (22.2%) Placebo Males and Females (22.5%)
GHBA 436 (PROVED Trial)	Double-blind, placebo-controlled, parallel, multicenter study	Daily dose: 0.125, 0.25, 0.375, or 0.5 mg Tablets with Diuretic Study duration: Minimum of 12 weeks	Total: 88 patients Digoxin- 42 patients Placebo- 46 patients	Digoxin Mean age: 63.7 Range: 25.0-89.0 Placebo Mean age: 63.7 Range: 40.0-82.0	Digoxin Males: 38 Females: 4 Placebo Males: 37 Females: 9
GHBA 437 (RADIANCE Trial)	Randomized, double-blind, placebo-controlled, parallel, multicenter study	Daily dose: 0.125, 0.25, 0.375, or 0.5 mg Tablets with Angiotensin Converting Enzyme Inhibitor and Diuretic Study duration: 12 weeks	Total: 178 patients with NYHA class II or III heart failure previously treated with digoxin, a diuretic, and an ACE inhibitor Digoxin- 85 patients Placebo- 93 patients	Digoxin Mean age: 61.4 Range: 34.0-84.0 Placebo Mean age: 59.2 Range: 24.0-82.0	Digoxin Males: 60 Females: 25 Placebo Males: 76 Females: 17

Study results

Table 9 - Results of Controlled Clinical Trials for Digoxin in Congestive Heart Failure

Primary Endpoints	Associated value and statistical significance for Drug and Placebo at specific dosages
DIG Trial	

Primary outcome: mortality. Seco ndary outcomes were mortality from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes, in particular suspected digoxin toxicity.	There were 1181 deaths (34.8%) in the digoxin group and 1194 deaths (35.1%) in the placebo group. There was a trend toward a decrease in the risk of death attributed to worsening heart failure (risk ratio, 0.88, 95 % confidence interval, 0.77 to 1.01; P=0.06). There were 6% fewer hospitalizations overall in the digoxin group than in the placebo group, and fewer patients were hospitalized for worsening heart failure (26.8% vs. 34.7%; risk ratio, 0.72; 95% confidence interval, 0.66 to 0.79; P<0.001).
GHBA 436 (PROVED Trial)	
Primary objectives were to evaluate the effects of the withdrawal of digoxin on: (1) exercise tolerance, and (2) the rate of withdrawal from the trial due to worsening of CHF in patients with NYHA Class II-III CHF who were in normal sinus rhythm and receiving concomitant therapy with diuretics.	Patients withdrawn from digoxin therapy showed worsened maximal exercise capacity (median change in exercise time -96 s) compared with that of patients who continued to receive digoxin (change in exercise time +4.5 s) (p = 0.003). Patients withdrawn from digoxin therapy showed an increased incidence of treatment failures (p = 0.039) (39%, digoxin withdrawal group vs. 19%, digoxin maintenance group) and a decreased time to treatment failure (p = 0.037). In addition, patients who continued to receive digoxin had a lower body weight (p = 0.044) and heart rate (p = 0.003) and a higher left ventricular ejection fraction (p = 0.016).
GHBA-437 (RADIANCE Trial)	
Primary objectives were to evaluate the effects of the withdrawal digoxin on exercise tolerance and on the rate of withdrawal from the trial due to worsening of CHF in patients with NYHA Class II-III CHF who were in normal sinus rhythm receiving concomitant therapy with diuretics and an ACE inhibitor. Endpoint was the last measurement obtained during the double-blind digoxin withdrawal period for each patient.	Worsening heart failure necessitating withdrawal from the study developed in 23 patients switched to placebo, but in only 4 patients who continued to receive digoxin (P<0.001). The relative risk of worsening heart failure in the placebo group as compared with the digoxin group was 5.9 (95 percent confidence interval, 2.1 to 17.2). All measures of functional capacity deteriorated in the patients receiving placebo as compared with those continuing to receive digoxin (P = 0.033 for maximal exercise tolerance, P = 0.01 for submaximal exercise endurance, and P = 0.019 for New York Heart Association class). In addition, the patients switched from digoxin to placebo had lower quality-of-life scores (P = 0.04), decreased ejection fractions (P = 0.001), and increases in heart rate (P = 0.001) and body weight (P<0.001).

DETAILED PHARMACOLOGY

Inhibition of Sodium-Potassium – ATPase:

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium.

Positive Iontropic Effect:
Both sodium and calcium ions enter cardiac muscle cells during each cycle of depolarization, contraction, and repolarization. The greater the amount of activating calcium, the greater the force of the contraction.

Electrophysiological Actions:

Atrial and ventricular muscle and specialized cardiac pacemaker and conduction fibers exhibit differing responses and sensitivities to cardiac gycosides that are a summation of the direct effects of these drugs on cardiac cells and their indirect, neurally mediated effects. At therapeutic, nontoxic serum or plasma concentrations (1 to 2 ng/mL), digoxin decreases automaticity and increases maximal diastolic resting membrane potential predominantly in atrioventricular (AV) nodal tissues, due to an increase in vagal tone and a decrease in sympathetic nervous system activity. There also is a prolongation of the effective refractory period and a decrease in conduction velocity in AV nodal tissue. At higher concentrations, this may cause sinus bradycardia or arrest and or prolongation of AV conduction or heart block.

MICROBIOLOGY

No microbiology studies were conducted with digoxin.

TOXICOLOGY

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrPMS-DIGOXIN®

Prpms-DIGOXIN® Digoxin Tablets, C.S.D. (0.0625, 0.125 & .250 mg)

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

ABOUT THIS MEDICATION

What the medication is used for:

This medicine is used for patients who have congestive heart failure. Heart failure, results when the heart cannot pump blood well enough to supply the body's needs. As a result, circulation becomes poor, and fluid can build up in the lungs and legs. This medicine can also be used in patients with fast heart rate or irregular heart rhythm. If you have a rapid or irregular heart beat, such as atrial fibrillation (sometimes called "a-fib"), digoxin can slow down and control your heart rate.

What it does:

If you have heart failure, digoxin can improve your heart's ability to pump blood. Better pumping of the heart will often improve symptoms such as shortness of breath. As a result, you may find it easier to go about your daily activities.

When it should not be used:

- If you have ever had any unusual or allergic reaction to digoxin medicines

What the medicinal ingredient is:

Digoxin

What the important nonmedicinal ingredients are:

Tablets: Corn Starch, D&C Yellow #10, FC&C Yellow #6, Lactose (hydrous), Magnesium Stearate, Pregelatinized Starch

What dosage forms it comes in:

Tablets, C.S.D.:

- 0.0625 mg
- 0.125 mg
- 0.25 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Do not take other prescription, non-prescription and herbal medications without advice from your doctor.**

Although digoxin has been prescribed to help some patients lose weight, it should *never* be used in this way. When used improperly, digoxin can cause serious problems.

BEFORE you use PrPMS-DIGOXIN® talk to your doctor or pharmacist if:

- You are pregnant or could become pregnant during treatment. Digoxin crosses the placenta and should not be used in pregnant women unless absolutely needed;
- You are breast-feeding-Digoxin is distributed into breast milk; caution should be used
- You are taking any other prescription, non-prescription and herbal medication.
- you are over 65 years of age, you may be more likely to experience side effects from digoxin. You may require a dosage adjustment or special monitoring.
- you have ever had any unusual or allergic reaction to digitalis medicines

The presence of other medical problems may affect the use of digitalis medicines. Make sure you tell your doctor if you have any other medical problems, especially:

- Electrolyte disorders (Imbalance in bodily salts)
- Heart disease
- Lung disease (severe)
- Heart rhythm problems
- Kidney disease
- Liver disease
- Thyroid disease

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with pms-DIGOXIN include:
- another medication for irregular heartbeats, such as quinidine, amiodarone, or propafenone;
- an antacid or laxative that contains aluminum, magnesium, or kaolin-pectin such as Maalox, Rolaids, Mylanta, Milk of Magnesia, and others;
- a beta-blocker such as atenolol, propranolol, acebutolol, metoprolol, labetalol or nadolol;
- a calcium channel blocker such as diltiazem amlodipine, felodipine, nifedipine, verapamil and others;
- a cancer chemotherapy drug;
- a diuretic (water pill) such as hydrochlorothiazide, chlorothiazide, chlorthalidone, furosemide, triamterene, amiloride, spironolactone and others;
- a steroid medicine such as prednisone, methylprednisolone, prednisolone, dexamethasone, and others;
- a thyroid medication;
- amphotericin B
- cholestyramine or colestipol;
- erythromycin or clarithromycin;
- indomethacin
- itraconazole
- metoclopramide (Reglan);
- rifampin
- sulfasalazine or
- tetracycline

Herbal products that may interact with pms-DIGOXIN (e.g. St. John's Wort)

You may require a dosage adjustment or special monitoring if you are taking any of the medicines listed above.

Drugs other than those listed here may also interact with digoxin or affect your condition. Talk to your doctor and pharmacist before taking any prescription or over-the-counter medicines, including herbal products.

PROPER USE OF THIS MEDICATION

Usual dose:
- Take digoxin exactly as directed by your doctor. If you do not understand these directions, ask your pharmacist, nurse, or doctor to explain them to you.
- Take each dose with a full glass of water.
- Try to take digoxin at the same time every day.
- Ask your doctor to teach you how to monitor your heart rate and at what heart rate you should notify them before taking any more medication.
- Do not stop taking digoxin without talking to your doctor. Stopping suddenly could make your condition worse. Even if you feel better, you may need to keep taking this medication to help the heart work properly.
- Make sure you always have enough digoxin on hand for vacations and holidays.
- Your doctor may want to perform blood tests during treatment with digoxin to monitor the amount of medication in your body.
- This medicine has been tested in children. Dosages should be individualized as directed by your doctor.
- It may take several weeks to several months for digoxin to improve your heart function. Don't be surprised if your symptoms don't get better right away. Keep taking your digoxin as prescribed. Digoxin is used to treat heart conditions that last for a long time, so you may take digoxin the rest of your life. Call your doctor if you have any problems with the drug.
- Dosage reduction may be required in patients with renal function impairment.

Overdose:
- Seek emergency medical attention.
- Symptoms of a digoxin overdose include nausea, vomiting, decreased appetite, diarrhea, confusion, seizures, hallucinations, light "halos" around objects, green or yellow vision, fatigue, irregular heartbeats, and abnormally fast or slow heartbeats.

Missed Dose:
Take the missed dose up to 12 hours late. If more than 12 hours have passed, skip the missed dose and take only the next regularly scheduled dose. **Do Not** take a double dose of this medication. Tell your doctor if you have missed 2 or more days of pms-DIGOXIN.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- If you experience any of the following side effects, talk to your doctor if you experience:
  - · depression;
  - · decreased sex drive; or
  - · enlarged breasts in males.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
· an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);			✓
· a severe headache, fainting, or extreme drowsiness or dizziness;		✓	
· irregular heartbeats;		✓	
· slow heartbeats (fewer than 60 beats per minute);		✓	
· abnormally fast heartbeats;		✓	
· vision changes (e.g., yellow-green or blurred vision);		✓	
· hallucinations; or		✓	
· abnormal or psychotic behaviour.		✓	
- decreased appetite and diarrhea;		✓	
- unusual tiredness or weakness;		✓	
- nausea or vomitting		✓	

This is not a complete list of side effects. For any unexpected effects while taking pms-DIGOXIN Tablets, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15°-30° in a dry place and protect from light. Avoid exposure to excessive heat. Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Pharmascience Inc., at 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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