PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrJAMP Digoxin

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

Manufacturer's Standard

Cardiotonic Glycoside

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JAMP Digoxin (Digoxin Tablets) are indicated for:

- **Congestive Heart Failure:** JAMP Digoxin is indicated for the treatment of mild to moderate heart failure. JAMP 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, JAMP 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:**
  JAMP Digoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

1.1 Pediatrics

Pediatrics (under 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of digoxin in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustments for Special Populations; 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics; 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Pediatrics.

1.2 Geriatrics

Geriatrics (over 70 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics; 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Geriatrics.

2 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 JAMP Digoxin.
- Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

JAMP Digoxin is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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:

- The body weight of the patient. Doses should be calculated based upon (i.e., ideal) body weight.
- The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
- 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).
- Concomitant disease states, concurrent medication or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see 7 WARNINGS AND PRECAUTIONS).
- To minimize toxic side effects, the lowest effective dose should be used as the maintenance dose.

4.2 Recommended Dose and Dosage Adjustment

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:

- Analytical problems in the assay procedure.
- Inappropriate serum sampling time.
- Administration of a digitalis glycoside other than digoxin.
- Conditions (described in 7 WARNINGS AND PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.
- 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.

- 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.

- 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 mcg/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 mcg/kg) (see 7 WARNINGS AND 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 0.5 to 0.75 mg (500 to 750 mcg) of digoxin tablets usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 0.125 to 0.375 mg (125 to 375 mcg) may be given cautiously at 6 to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of digoxin tablets that a 70-kg patient requires to achieve 8 to 12 mcg/kg peak body stores is 0.75 to 1.25 mg (750 to 1250 mcg).

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 10 CLINICAL PHARMACOLOGY , Table 6).

Table 1 Usual Daily Maintenance Dose Requirements of digoxin tablets (mg) for Estimated Peak Body Stores of 10 mcg/kg

Corrected Ccr (mL/min per 70 kg)*	Body Weight (kg)						Number of Days Before Steady State Achieved**
	50	60	70	80	90	100	
0	0.0625	0.125	0.125	0.125	0.1875	0.187.5	22
10	0.125	0.125	0.125	0.1875	0.1875	0.187.5	19
20	0.125	0.125	0.1875	0.1875	0.1875	0.25	16
30	0.125	0.1875	0.1875	0.1875	0.25	0.25	14
40	0.125	0.1875	0.1875	0.25	0.25	0.25	13
50	0.1875	0.1875	0.25	0.25	0.25	0.25	12
60	0.1875	0.1875	0.25	0.25	0.25	0.375	11
70	0.1875	0.25	0.25	0.25	0.25	0.375	10
80	0.1875	0.25	0.25	0.25	0.375	0.375	9
90	0.1875	0.25	0.25	0.25	0.375	0.5	8
100	0.25	0.25	0.25	0.375	0.375	0.5	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 1, 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 mcg (0.25 mg) daily of 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.

Dosage Adjustments for Special Populations

Elderly

Given the higher incidence of concomitant illness (renal, hepatic and cardiovascular) and concomitant medication in the elderly, JAMP Digoxin should be used with caution in this population. See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics.

Pediatrics

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 2 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 2 Daily Maintenance Doses of JAMP Digoxin Tablets in Children with Normal Renal Function

Age	Daily Maintenance Dose mg / kg (mcg/kg)
2 to 5 years	0.01 to 0.015 (10 to 15)
5 to 10 years	0.007 to 0.01 (7 to 10)
Over 10 years	0.003 to 0.005 (3 to 5)

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.

4.4 Administration

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

4.5 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 to take it 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.

5 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 below), 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 may be 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 bradyarrhythmia or heart block. The administration of more than 10 mg of digoxin in a previously healthy adult, 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.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength	All Non-medicinal Ingredients
Oral	Tablets: 0.0625 mg, 0.125 mg and 0.25 mg	Tablets: **0.0625 mg:** FD&C Yellow No. 6, Hydroxypropyl cellulose, Lactose monohydrate , Magnesium Stearate, Pregelatinized starch, **0.125 mg:** D&C Yellow No. 10, Hydroxypropyl cellulose, Lactose monohydrate , Magnesium Stearate, Pregelatinized starch, Yellow Ferric Oxide,. **0.25 mg:** Hydroxypropyl cellulose , Lactose monohydrate , Magnesium Stearate, , Pregelatinized starch

JAMP Digoxin
(Digoxin Tablets):

0.0625 mg: Each round, peach colored, flat-face bevelled edge tablet debossed with "D1" on one side, contains: digoxin 0.0625 mg (62.5 mcg).
Bottles of 100 tablets.

0.125 mg: Each round, yellow colored, flat-face bevelled edge tablet debossed with "D2" on one side, contains: digoxin 0.125 mg (125 mcg). Bottles of 100 tablets.

0.25 mg: Each round, white colored, biconvex tablet debossed with "D3" on one side, contains: digoxin 0.25 mg (250 mcg). Bottles of 250 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

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. JAMP DIGOXIN 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.

Multifocal Atrial Tachycardia:
Digoxin should not be used for the treatment of multifocal atrial tachycardia.

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 5 OVERDOSAGE).

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 related 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.

Monitoring and Laboratory Tests

Patients receiving JAMP Digoxin 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 **4 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.

Renal

Patients with Renal Disease:
Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see 4 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 4 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.

7.1 Special Populations

7.1.1 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

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.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adults

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 central nervous system (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 tablets 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.

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 (ECG) 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 7 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, delirium, 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.

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.

8.2 Clinical Trial Adverse Reactions

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

Table 4 summarizes the incidence of adverse experiences 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 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 enrolment.

Table 4 Adverse Experiences in Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials with Digoxin Tablets (Number of Patients Reporting)

	Digoxin Tablets n=123 (%)	Placebo n=125 (%)
Cardiovascular		
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)

8.3 Less Common Clinical Trial Adverse Reactions

Gastrointestinal: Abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

Other: Thrombocytopenia, maculopapular rash and other skin reactions.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Caution should be exercised when digoxin and saquinavir are co-administered (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 5, Protease Inhibitors).

9.2 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 can 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, cholestyramine, 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 co-administered 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.

9.3 Drug- Behavioural 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.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 Established or Potential Drug-Drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical Comment

Albuterol	CT	Concurrent use may result in decreased 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.	Serum digoxin concentrations should be monitored because mean decreases of 16-22% in serum digoxin were observed after single dose of albuterol (I.V. or per os) to normal volunteers who had received digoxin for 10 days.
Alprazolam	C, CT	Concurrent use may result in digoxin toxicity (nausea, vomiting, diarrhea, arrhythmias, persistent headache, confusion, fainting, visual disturbances), possibly by decreasing the renal clearance of digoxin.	Monitor for signs of digoxin intoxication, if symptoms are present, obtain digoxin level and reduce dose accordingly.
Amiodarone	C, CT	Concurrent use may result in digoxin toxicity (nausea, vomiting, arrhythmias). Increases in serum digoxin concentrations by as much as 100% have been reported with concurrent use. 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.	When amiodarone is administered to patients taking digoxin, consider discontinuing digoxin, or reduce the digoxin dose by approximately 50%. If digoxin is continued, closely monitor serum digoxin levels and clinical evidence of digoxin toxicity.
Antacids or antidiarrheal adsorbents (e.g., kaolin and pectin) or sulfasalazine	CT	Concurrent use may result in decreased digoxin levels and effectiveness by decreasing bioavailability.	Serum levels of digoxin should be monitored. The dosing intervals of antacids/antidiarrheal adsorbents and digoxin may be separated by approximately 2 hours to avoid sequelae of possible drug interaction.
Antibiotics, oral, especially macrolide antibiotics, such as: clarithromycin or erythromycin or tetracycline	C, CT	Concurrent use of some oral antibiotics may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result from increased serum concentrations (nausea, vomiting, arrhythmias).	Close monitoring of digoxin serum concentration and digoxin toxicity is recommended when antibiotic therapy is added or removed. Dose adjustment may be required.

Anticancer medications (such as bleomycin, cyclophosphamide, cytarabine, doxorubicin, procarbazine, vandetanib and vincristine) or radiation therapy	C, CT	Concurrent use may decrease digoxin absorption and bioavailability due to temporary damage of the GI mucosa and which may continue for several days after treatment.	Closely monitor serum digoxin concentrations when administered concomitantly with chemotherapeutic combination therapies. Also monitor patients for response to digoxin. A dosage form with greater bioavailability, such as the capsule or solution may help to minimize decreased bioavailability.
Atorvastatin	CT	Concurrent use may increase digoxin plasma concentrations; steady-state serum concentration increases of approximately 20% have been reported.	Carefully monitor digoxin levels and cardiac effects. Adjustment of digoxin dose may be required.
Beta-adrenergic blocking agents including atenolol, carvedilol, metoprolol and propranolol	CT	Both digoxin and beta-blockers slow atrioventricular conduction and decrease heart rate, and concurrent use can increase the risk of bradycardia and possible digoxin toxicity. 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.	Monitor heart rate and PR interval and use with caution. Plasma digoxin concentrations should be monitored.
Bran fiber, dietary	CT	When oral digoxin is taken with food, the absolute bioavailability of digoxin is reduced, but the extent of absorption is unchanged. The amount of digoxin absorbed from an oral digoxin dose may be reduced when taken with meals high in bran fiber.	Administering oral digoxin consistently with relationship to meals and avoiding high-fiber foods concomitantly should be considered.
Bupropion	CT	Bupropion (extended-release, 150 mg) administered ~24 hours before digoxin, decreases digoxin AUC0-24h by 40% and increases digoxin renal clearance by 80% in healthy volunteers.	Serum digoxin concentrations should be monitored and dosages adjusted accordingly.

Calcium channel blocking agents, especially bepridil, diltiazem, nifedipine or verapamil	C, CT	Concurrent use result in increased serum digoxin concentrations and digoxin toxicity (nausea, vomiting, arrhythmias). Verapamil may increase serum digoxin concentrations by 50% to 75%; bepridil may increase serum digoxin concentrations by approximately 34%; some studies have reported no interaction with diltiazem while other have reported increases in plasma 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. Concurrent use with calcium channel blocking agents has additive effects on AV nodal conduction, which could result in complete heart block.	Monitor patient serum digoxin concentrations and for signs or symptoms of digoxin toxicity. Adjust dose as required particularly when co-administered with verapamil in patients with hepatic cirrhosis as this effect may be magnified. In patients with mild ventricular dysfunction, optimum doses of digitalis and/or diuretics should be established prior to initiating diuretics. If diuretic is stopped after concurrent therapy, digoxin levels should be monitored and doses adjusted accordingly, to avoid under-digitalization.
Cholestyramine or colestipol	C, CT	Concurrent use may delay and reduce the absorption of digoxin.	Administer digoxin two hours before or four to six hours after cholestyramine or colestipol, or separate administration times as much as possible. Monitor digoxin serum levels closely and observe the patient for changes in response to digoxin. Digoxin dosage adjustments may be necessary.
Cyclosporine	C	Concurrent use has resulted in digoxin increased concentrations, which may lead to digoxin toxicity (nausea, vomiting, arrhythmias).	Closely monitor serum digoxin levels within three to five days of initiating or discontinuing cyclosporine if toxicity is observed.
Diphenoxylate or propantheline	CT	Concurrent use may result in increased serum digoxin levels, due to increased digoxin absorption.	Monitor digoxin serum levels. Adjust the digoxin dose if necessary.

Diuretics, potassium-depleting (such as bumetanide, ethacrynic acid, furosemide, indapamide, mannitol, or thiazides) or hypokalemia-causing medications	C, CT	Concurrent use may result in digoxin toxicity (nausea, vomiting, arrhythmias) due to decreases in serum potassium concentrations.	Frequent monitoring of electrolytes (i.e., potassium, magnesium) with appropriate replacement is recommended.
Dronedarone	C	The concomitant use of digoxin and dronedarone is generally not recommended. Patients should be treated with digoxin and dronedarone only if there is a specific therapeutic need and no alternative treatment available.	These patients should be closely monitored for serum digoxin levels, especially during the first week of co-administration. Clinical and ECG monitoring are also recommended, and the digoxin dose should be adjusted as appropriate.
Flecainide	CT	Concurrent use may result in digoxin toxicity (nausea, vomiting, arrhythmias). Concurrent use has increased serum digoxin concentrations, on average by 24%; it has also been speculated that concurrent use may cause a slight additive increase in the PR interval.	Decreasing the digoxin dose or treatment discontinuation may be necessary. Monitor ECG and serum digoxin levels.
Hepatic enzyme inducers, such as: barbiturates, phenytoin or rifampin	C, CT	Concurrent use may result in decreased digoxin levels by 50%.	Monitor digoxin levels and adjust dosage accordingly.
Indomethacin	C, CT	Concurrent use may result in digoxin toxicity (nausea, vomiting, arrhythmias) possibly by inhibiting the renal elimination of digoxin. 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.	Monitor serum digoxin levels and signs of toxicity such as nausea, vomiting, or changes in mental status. When using this combination in premature infants, monitor serum digoxin levels and ECGs frequently to detect digoxin toxicity early and adjust dosage accordingly or discontinue treatment.

Itraconazole	C, CT	Concurrent use may result in increased risk of digoxin toxicity (nausea, vomiting, cardiac arrhythmias) possibly by decreasing renal elimination. Serum digoxin concentration increases of approximately 50% have been reported.	Serum digitalis concentrations should be monitored, and dosage adjusted accordingly.
Metoclopramide	C, CT	Concurrent use may result in decreased digoxin levels. Serum digoxin concentrations as determined by AUC have been reported to decrease by about 24%.	Serum digitalis concentrations should be monitored.
Neomycin	CT	Concurrent use results in decreased digoxin levels. 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.	Monitor digoxin levels when neomycin is administered on a chronic basis. Unexpectedly low serum digoxin concentrations may result. It is recommended that digoxin and neomycin administration be separated by at least 8 hours.
Omeprazole	C, CT	Concurrent use may result in an increased risk of digoxin toxicity (nausea, vomiting, arrhythmia). On average, C_{max} and AUC values have been reported to be about 10% higher with concurrent use.	Monitor digoxin levels and signs and symptoms of digoxin toxicity.
Propafenone	CT	Concurrent use results in digoxin toxicity (nausea, vomiting, arrhythmias). Increase in serum digoxin concentrations ranging from 35 to 85% was documented.	Monitor digoxin levels when initiating, changing dose, or discontinuing propafenone during concomitant digoxin therapy.
Protease inhibitors, such as: cobicistat, saquinavir/ritonavir and simeprevir	CT	Concurrent use may result in increased digoxin exposure (AUC ↑40%, C_{max} ↑30-40%). Caution should be exercised when these drugs and digoxin are coadministered.	Closely monitor digoxin levels and signs of digoxin toxicity and used for titration of digoxin dose to obtain the desired clinical effects. The dose of digoxin may need to be reduced. The lowest dose of digoxin should initially be prescribed.
Quinidine or quinine	C, CT	Concurrent use results in increased digoxin plasma concentrations. 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.	Closely monitor serum digoxin levels, signs of digoxin toxicity and adjust dosage as necessary.

Spironolactone	CT	Concurrent use may result in increased digoxin exposure (by one third) and toxicity.	Upon initiation of spironolactone in patients receiving digoxin therapy, a 15% to 30% decrease in digoxin dosage or modification of the dosing frequency is recommended. Spironolactone may be incorrectly detected as digoxin at levels up to 0.5 ng/mL, resulting in falsely elevated digoxin levels. Monitor patients for signs of toxicity.
Succinylcholine	C, CT	Concurrent use may result in an increased risk of arrhythmias due to a sudden release of potassium from muscle cells.	Serum digitalis concentrations should be monitored, and dosages adjusted accordingly.
Sucralfate	C	Concurrent use may result in decreased digoxin effectiveness. Sucralfate was reported to reduce digoxin plasma concentrations by about 19% by reducing its bioavailability.	Sucralfate should be taken at least 2 hours after digoxin if concurrent use cannot be avoided.
Sympathomimetics	T	Concurrent use may increase the risk of cardiac arrhythmias (cardiotoxicity).	Closely monitor signs of cardiotoxicity. Serum digitalis concentrations should be monitored, and dosages adjusted accordingly.
Thyroid hormones	C, CT	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.	Plasma digoxin levels should be monitored in all patients with thyroid dysfunction who require digoxin therapy. Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Increase in digitalis dose may be required with the use of thyroid hormones in a hyperthyroid patient or dosage or reduced in a hypothyroid patient.

Legend: C: Case; CT: Clinical Trial, T: Theoretical

9.5 Drug-Food Interactions

The amount of digoxin absorbed from an oral digoxin dose may be reduced when taken with meals high in bran fiber. See 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 6, Bran fiber, dietary.

9.6 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.

9.7 Drug-Laboratory Test 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.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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 tablets

are shown in Table 6.

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

Product	Time to Onset of Effect*	Time to peak Effect*
Digoxin Tablets	0.5 to 2 hours	2 to 6 hours

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

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 Inotropic 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 glycosides 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.

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.

10.3 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 post-distribution serum levels are in equilibrium with tissue levels and correlate with pharmacologic effects. In individual patients, these post-distribution 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 metabolized, several metabolites of digoxin 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.

Elimination

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 1 month of age generally require proportionally larger doses than adults on the basis of body weight or body surface area (see 4 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.

- **Sex:**
  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.

- **Genetic Polymorphism:**
  The effect of genetic polymorphism on the pharmacokinetics of digoxin tablets was not studied.

- **Ethnic Origin:**
  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.

11 STORAGE, STABILITY AND DISPOSAL

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

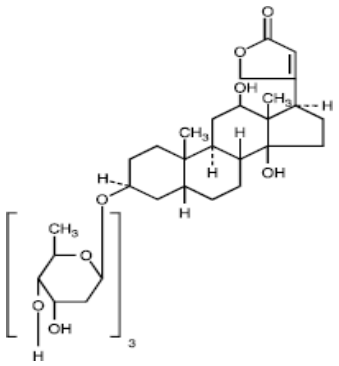
Drug Substance

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-5-card-20(22)-enolide

Molecular formula and molecular mass: $C_{41}H_{64}O_{14}$; 780.95 g/mol

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.

14 CLINICAL TRIALS

14. 1 Trial Design and Study Demographics

Table 7 Summary of Patient Demographics for clinical Trials in Congestive Heart Failure

Study #	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
Digitalis Investigation Group (DIG Trial)	Randomized, double-blind, placebo-controlled	Daily dose: 0.125 - 0.500 mg tablets (median dose 0.25 mg) Study duration: Range from 28 to 58 months (mean duration 37 months)	Total: 7788 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 63.4 yrs. (63.4 ± 11.0) Placebo 63.5 yrs. (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 63.7 yrs. (25.0-89.0) Placebo 63.7 yrs. (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 61.4 yrs. (34.0-84.0) Placebo 59.2 yrs. (Range: 24.0-82.0)	Digoxin Males: 60 Females: 25 Placebo Males: 76 Females: 17

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 # 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, and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg.

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.

14.2 Study Results

Table 8 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. Secondary 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).

RADIANCE and PROVED Trials

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 RADIANCE study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller PROVED trial, these trended in favour of a treatment benefit.

DIG Trial

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 increased 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 10. 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 9 Subgroup Analyses of Mortality and Hospitalization during the First Two Years Following Randomization in the DIG Trial

		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.

14.3 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of JAMP DIGOXIN 0.25 mg tablets (JAMP Pharma Corporation) and PrTOLOXIN® 0.25 mg tablets (PENDOPHARM, Division of Pharmascience Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 25 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Digoxin (1 x 0.25 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72}[3] (ng·h/mL)	14.68 14.62 (16.47)	14.86 15.19 (17.85)	98.8	91.4 – 106.9
C_{max} (ng/mL)	1.37 1.45 (32.23)	1.41 1.55 (45.30)	97.4	83.7 – 113.5
T_{max}[4] (h)	1.00 (0.50 – 2.67)	0.75 (0.50 – 1.75)		

[1] JAMP DIGOXIN (digoxin) tablets, 0.25 mg (JAMP Pharma Corporation)
[2] PrTOLOXIN® (digoxin) tablets, 0.25 mg (PENDOPHARM, Division of Pharmascience Inc.)
[3] n=20 for the Test product and n=22 for the Reference product
[4] Expressed as median (range) only

Due to the long elimination half-life of digoxin, AUC_I and $T_{1/2}$ could not be accurately calculated from the data obtained in this study.

A randomized, two-way, single-dose, crossover comparative bioavailability study of JAMP DIGOXIN 0.25 mg tablets (JAMP Pharma Corporation) and PrTOLOXIN® 0.25 mg tablets (PENDOPHARM, Division of Pharmascience Inc.) was conducted in healthy, adult, male subjects under high-fat, high-calorie fed conditions. Comparative bioavailability data from 40 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Digoxin (1 x 0.25 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72}[3] (ng·h/mL)	13.61 13.79 (16.36)	13.76 13.89 (13.70)	98.8	95.9 – 101.8

Digoxin (1 x 0.25 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
C_{max} (ng/mL)	1.02 1.07 (29.41)	1.08 1.12 (25.95)	94.4	87.2 – 102.3
T_{max}[4] (h)	1.25 (0.50 – 3.33)	1.50 (0.50 – 3.00)		

[1] JAMP DIGOXIN (digoxin) tablets, 0.25 mg (JAMP Pharma Corporation)
[2] PrTOLOXIN® (digoxin) tablets, 0.25 mg (PENDOPHARM, Division of Pharmascience Inc.)
[3] n=37 for the Reference product
[4] Expressed as median (range) only

Due to the long elimination half-life of digoxin, AUC_I and $T_{1/2}$ could not be accurately calculated from the data obtained in this study.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether digoxin affects fertility in males or females.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrTOLOXIN® (Digoxin Tablets; 0.0625, 0.125 and 0.25 mg) Product Monograph, PENDOPHARM, Division of Pharmascience Inc.; Control Number #246803, Date of Revision: May 12, 2021.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrJAMP Digoxin
Digoxin Tablets

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

Serious Warnings and Precautions

- While taking JAMP Digoxin, do not take other prescription, non-prescription or herbal medications without talking to your healthcare professional.

What is JAMP Digoxin 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 a fast or irregular heartbeat , such as atrial fibrillation (sometimes called "a-fib").

How does JAMP Digoxin work?

JAMP Digoxin contains the medicinal ingredient digoxin. 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.
If you have a fast or irregular heartbeat, digoxin can slow down and control your heart rate.

What are the ingredients in JAMP Digoxin?

Medicinal ingredients: digoxin

Non-medicinal ingredients: D&C Yellow No. 10 (0.125 mg tablets), FD&C Yellow No. 6 (0.0625 mg tablets), Lactose monohydrate, Magnesium stearate, Pregelatinized starch, Hydroxy propyl cellulose, Yellow Ferric Oxide (0.125 mg tablets).

JAMP Digoxin comes in the following dosage forms:

Tablets: 0.0625 mg, 0.125 mg, 0.25 mg

Do not use JAMP Digoxin if you:

- have an irregular heartbeat called “ventricular fibrillation”
- have ever had any unusual or allergic reaction to digoxin medicines, including JAMP Digoxin, or any of the nonmedicinal ingredients in JAMP Digoxin (see What are the ingredients in JAMP Digoxin?)

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

- are dehydrated or suffer from excessive vomiting, diarrhea or sweating (electrolyte disorder)
- have heart problems
- have severe lung disease
- have liver or kidney problems
- have thyroid problems
- are pregnant or could become pregnant. JAMP Digoxin should not be used in pregnant women unless absolutely needed
- are breast-feeding. JAMP Digoxin passes into breast milk
- are over 65 years of age. You may be more likely to experience side effects from JAMP Digoxin. Your healthcare professional may have to adjust your dose or monitor you more closely.
- are lactose intolerant or have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  because lactose is a non-medicinal ingredient in JAMP Digoxin.

Other warnings you should know about:

Although digoxin, the medicinal ingredient in JAMP Digoxin, has been used to help some patients lose weight, it should never be used in this way. When used improperly, digoxin can cause serious side effects that can, in some cases, be fatal.

Your healthcare professional may need to do blood tests to make sure you are taking the right dose. They might also need to do bloodwork to check on your overall health since JAMP Digoxin can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

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

Serious Drug Interactions

- Your healthcare professional will need to monitor you closely if you are taking JAMP Digoxin with medicines used to treat HIV infection and AIDS, such as cobicistat, saquinavir/ ritonavir and simeprevir.

The following may interact with **JAMP Digoxin:**

- other medicines used to treat irregular heartbeat, such as dronedarone, quinidine, amiodarone, propafenone
- antacids or laxatives that contain aluminum, magnesium, or kaolin-pectin, such as Maalox, Rolaids, Mylanta, milk of magnesia. These products should be taken either 2 hours before or 2 hours after JAMP Digoxin.

- sucralfate, a medicine used to treat and prevent ulcers. JAMP Digoxin should be taken at least 2 hours before sucralfate.
- bupropion, a medicine used to treat depression
- medicines used to lower blood pressure called beta-blockers (such as atenolol, propranolol, acebutolol, metoprolol, labetalol, nadolol) and calcium channel blockers (such as diltiazem, amlodipine, felodipine, nifedipine, verapamil)
- cancer chemotherapy drugs (such as bleomycin, cyclophosphamide, cytarabine, doxorubicin, procarbazine, vandetanib, vincristine) and radiation therapy
- cyclosporine, a medicine used to supress the immune system
- diuretics (water pills), such as hydrochlorothiazide, chlorothiazide, chlorthalidone, furosemide, triamterene, amiloride, spironolactone
- steroid medicine, such as prednisone, methylprednisolone, prednisolone, dexamethasone
- thyroid hormones, used to treat thyroid problems
- cholestyramine and colestipol, medicines used to lower high cholesterol. JAMP Digoxin should be taken either 2 hours before or 4 to 6 hours after these medicines
- antibiotics, medicines used to treat bacterial infections, such as erythromycin, tetracycline, clarithromycin, neomycin
- indomethacin, a medicine used to treat gout
- medicines used to treat fungal infections, such as itraconazole, amphotericin B
- metoclopramide, a medicine used to prevent nausea
- rifampin, an antibiotic used to treat tuberculosis infection
- sulfasalazine, a medicine used to treat arthritis
- atorvastatin, a medicine used to lower high cholesterol
- albuterol, a medicine used to treat breathing problems
- alprazolam, a medicine used to treat mental health problems
- medicines used to treat stomach problems, such as diphenoxylate, propantheline, omeprazole
- barbiturates and phenytoin, medicines used to prevent seizures
- succinylcholine, a medicine used to relax the body during surgery
- St. John's wort, an herbal medicine used to treat depression

Your healthcare professional may need to adjust your dose or monitor you more closely if are taking any of the medicines listed above.

How to take JAMP Digoxin:

- Take JAMP Digoxin exactly as directed by your healthcare professional. If you do not understand the directions, ask your healthcare professional to explain them to you.
- Take JAMP Digoxin tablets with a full glass of water.
- Try to take JAMP Digoxin at the same time every day.
- Ask your healthcare professional to teach you how to monitor your heart rate and at what heart rate you should notify them before taking any more medication.
- Even if you feel better, do not stop taking JAMP Digoxin without talking to your healthcare professional. Stopping suddenly could make your condition worse.
- Make sure you always have enough JAMP Digoxin on hand for vacations and holidays.

- It may take several weeks to several months for JAMP Digoxin to improve your heart function. Don't be surprised if your symptoms don't get better right away. Keep taking your JAMP Digoxin as prescribed. JAMP Digoxin is used to treat heart conditions that last for a long time, so you may take JAMP Digoxin the rest of your life.

Usual dose:

Your healthcare professional will decide on your dose based on your weight, your age, how well your kidneys work, other medical conditions you might have, other medications you might be taking and how well you respond to JAMP Digoxin.

Overdose:

If you think you, or a person you are caring for, have taken too much JAMP Digoxin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Symptoms of overdose include nausea, vomiting, decreased appetite, diarrhea, confusion, seizures, hallucinations, light "halos" around objects, green or yellow vision, fatigue, irregular heartbeat, and abnormally fast or slow heartbeat.

Missed Dose:
Take the missed dose up to 12 hours late. If more than 12 hours have passed, skip the missed dose and go back to your regular dosing schedule. **Do not** take a double dose of this medication. Tell your healthcare professional if you have missed 2 or more days of JAMP Digoxin.

What are possible side effects from using JAMP Digoxin?

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

Side effects may include:

- decreased appetite
- nausea, vomiting, diarrhea
- stomach pain
- unusual tiredness or weakness
- headache
- dizziness
- decreased sex drive
- enlarged breasts in males
- rash

Serious side effects and what to do about them		
	Talk to your healthcare professional	**Stop taking drug and**

Symptom / effect	Only if severe	In all cases	get immediate medical help
FREQUENCY UNKNOWN			
Allergic reaction: rash, hives, difficulty breathing or swallowing, swelling of the throat, lips, tongue, or face			✓
Neurological problems: severe headache, fainting, extreme drowsiness, dizziness		✓	
Heart problems: irregular heartbeats, slow heartbeat (fewer than 60 beats per minute), abnormally fast heartbeat		✓	
Vision changes: yellow-green vision, blurred vision		✓	
Mental heath problems: hallucinations, depression, anxiety, abnormal behaviour, speech or thoughts		✓	

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

Reporting Side Effects

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

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

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

Storage:

Store at 15°C-30°C in a dry place. Avoid exposure to excessive heat.

Keep out of reach and sight of children.

If you want more information about JAMP Digoxin:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.jamppharma.com) ,or by calling 1-866-399-9091.

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