

CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

542401

LANOXICAPS® (DIGOXIN SOLUTION IN CAPSULES)

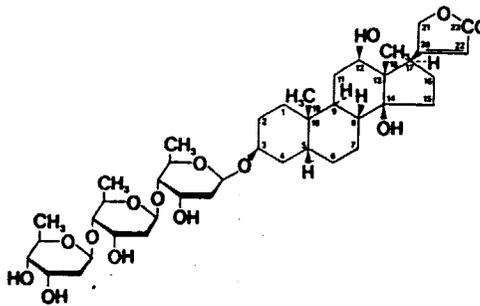
50 µg (0.05 mg) I.D. Imprint A2C (red)
 100 µg (0.1 mg)* I.D. Imprint B2C (yellow)
 200 µg (0.2 mg)* I.D. Imprint C2C (green)



DESCRIPTION: Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin has the empirical formula $C_{41}H_{64}O_{14}$, a molecular weight of 780.96 and melting and decomposition points above 235° 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. Digoxin powder is composed of odorless white crystals.

Digoxin has the chemical name: 3β-[(0-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-0-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4))-2,6-dideoxy-β-D-ribo-hexopyranosyl]oxy]-12β, 14-dihydroxy-5β-card-20(22)-enolide, and the structure shown.



Lanoxicaps is a stable solution of digoxin enclosed within a soft gelatin capsule for oral use. Each capsule contains the labeled amount of digoxin USP dissolved in a solvent comprised of polyethylene glycol 400 USP, 8 percent ethyl alcohol, propylene glycol USP and purified water USP.

CLINICAL PHARMACOLOGY:

Mechanism of Action: The influence of digitalis glycosides on the myocardium is dose-related, and involves both a direct action on cardiac muscle and the specialized conduction system, and indirect actions on the 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 sino-atrial (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: 1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); 2) a slowing of heart rate (negative chronotropic effect); and 3) decreased conduction velocity through the AV node. In higher doses, digitalis increases sympathetic outflow from the central nervous system (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.

Pharmacokinetics:

Absorption — Gastrointestinal absorption of digoxin is a passive process. Absorption of digoxin from Lanoxicaps capsules has been demonstrated to be 90 to 100% complete compared to an identical intravenous dose of digoxin. Conventional digoxin tablets are absorbed 60 to 80%. The enhanced absorption from Lanoxicaps compared to digoxin tablets and elixir is associated with reduced between-patient and within-patient variability in steady-state serum concentrations. The peak serum concentrations are higher than those observed after tablets. When digoxin tablets or capsules 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 fiber, however, the amount absorbed from an oral dose may be reduced. Comparisons of the systemic availability and equivalent doses for digoxin preparations are shown in the following table:

PRODUCT	BIOAVAILABILITY	EQUIVALENT DOSES (IN MG)*		
		0.125	0.25	0.5
Lanoxin [®] Tablet	60-80%	0.125	0.25	0.5
Lanoxin Elixir	70-85%	0.125	0.25	0.5
Lanoxin Injection/IM	70-85%	0.125	0.25	0.5
Lanoxin Injection/IV	100%	0.1	0.2	0.4
Lanoxicaps Capsules	90-100%	0.1	0.2	0.4

*1 mg = 1000 µg

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 (particularly high for digoxin capsules) 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 (see Serum Digoxin Concentrations in DOSAGE AND ADMINISTRATION section).

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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.

Pharmacologic Response — The approximate times to onset of effect and to peak effect of all the Lanoxin and Lanoxicaps preparations are given in the following table:

PRODUCT	TIME TO ONSET OF EFFECT*	TIME TO PEAK EFFECT*
Lanoxin [®] Tablet	0.5-2 hours	2-6 hours
Lanoxin Elixir	0.5-2 hours	2-6 hours
Lanoxin Injection/IM	0.5-2 hours	2-6 hours
Lanoxin Injection/IV	5-30 minutes†	1-4 hours
Lanoxicaps Capsules	0.5-2 hours	2-6 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effect and electrocardiographic changes.
† Depending upon rate of infusion.

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 intravenous 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 2.0 days. The half-life 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 by-pass because most of the drug is in tissue rather than circulating in the blood.

INDICATIONS AND USAGE:

Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma). Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients; corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, 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: Digoxin reduces ventricular rate and thereby improves hemodynamics. Palpitation, precordial distress or weakness are relieved and concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate.

Atrial Flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a controlled ventricular response. Digoxin treatment should be maintained if atrial fibrillation persists. (Electrical cardioversion is often the treatment of choice for atrial flutter. See discussion of cardioversion in PRECAUTIONS section.)

Paroxysmal Atrial Tachycardia (PAT): Digoxin may convert PAT to sinus rhythm by slowing conduction through the AV node. If heart failure has ensued or paroxysms recur frequently, digoxin should be continued. In infants, digoxin is usually continued for 3 to 6 months after a single episode of PAT to prevent recurrence.

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 digoxin. Hypersensitivity to 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: 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.

It is recommended that digoxin in soft capsules be administered in divided daily doses to minimize any potential adverse reactions, since peak serum digoxin concentrations resulting from the capsules are approximately twice those after bioequivalent tablet doses (400 µg of Lanoxicaps are bioequivalent to 500 µg of tablets). Studies are underway to determine if there are any increased risks associated with the higher peaks that occur with single daily dosing of soft gelatin capsules.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these 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 (see DOSAGE AND ADMINISTRATION section).

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 should be discontinued as soon as possible.

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.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: 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 section). 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.

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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 dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

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.

Quinidine causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the quinidine dose. Interestingly, both the digoxin clearance and the volume of distribution are reduced, so that the serum half-life may not change. Because of the considerable variability of this interaction, digoxin dosage should be carefully individualized.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

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.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

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.

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.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving 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 DOSAGE AND ADMINISTRATION section.

Drug Interactions: 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* causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. *Antacids*, *kaolin-pectin*, *sulfasalazine*, *neomycin* and *cholestyramine* 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 *propranolol* and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: Pregnancy Category C. 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. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: 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.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac — Unifocal or multifocal premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia 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.

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.

Gastrointestinal — Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms.

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CNS — Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

Other — Gynecomastia is occasionally 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.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial.

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

Due to the more complete absorption of digoxin from soft capsules, recommended oral doses are only 80 percent of those for Tablets, Elixir and I.M. Injection.

Because the significance of the higher peak serum concentrations associated with once daily capsules is not established, divided daily dosing is presently recommended for:

1. Infants and children under 10 years of age;
2. Patients requiring a daily dose of 300 µg (0.3 mg) or greater;
3. Patients with a previous history of digitalis toxicity;
4. Patients considered likely to become toxic;
5. Patients in whom compliance is not a problem.

Where compliance is considered a problem, single daily dosing may be appropriate.

In deciding the dose of digoxin, several factors must be considered:

1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

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 one and three weeks.

Adults:

Adults — 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. Larger stores (10 to 15 µg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. 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 section].

The loading dose should be based on the projected peak body stores and 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.

In previously undigitalized patients, a single initial Lanoxicaps dose of 400 to 600 µg (0.4 to 0.6 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 100 to 300 µg (0.1 to

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0.3 mg) may be given cautiously at 6 to 8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxicaps that a 70 kg patient requires to achieve 8 to 15 µg/kg peak body stores is 600 to 1000 µg (0.6 to 1.0 mg).

Although peak body stores are mathematically related to loading doses and are utilized to calculate maintenance doses, they do not correlate with measured serum concentrations. This discrepancy is caused by digoxin distribution within the body during the first 6 to 8 hours following a dose. Serum concentrations drawn during this time are usually not interpretable. 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:

$$\text{Maintenance Dose} = \text{Peak Body Stores (i.e. Loading Dose)} \times \frac{\% \text{ Daily Loss}}{100}$$

$$\text{Where: \% Daily Loss} = 14 + \text{Ccr}/5$$

Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m² 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.

A common practice involves the use of Lanoxin® Injection to achieve rapid digitalization, with conversion to Lanoxicaps or Lanoxin Tablets for maintenance therapy. If patients are switched from IV to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see table, CLINICAL PHARMACOLOGY section).

Adults — Gradual Digitalization with a Maintenance Dose: The following table provides average Lanoxicaps daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function:

Usual Lanoxicaps Daily Maintenance Dose Requirements (µg)
for Estimated Peak Body Stores of 10 µg/kg

	Lean Body Weight (kg/lbs)						
	50/110	60/132	70/154	80/176	90/198	100/220	
0	50	100	100	100	150	150	22
10	100	100	100	100	150	150	19
20	100	100	150	150	150	200	16
30	100	150	150	150	200	200	14
40	100	150	150	200	200	250	13
50	150	150	200	200	250	250	12
60	150	150	200	200	250	300	11
70	150	200	200	250	250	300	10
80	150	200	200	250	300	300	9
90	150	200	250	250	300	350	8
100	200	200	250	300	300	350	7

Example — based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min, should be given 200 µg (0.2 mg) of Lanoxicaps per day, usually taken as a 100 µg (0.1 mg) capsule after the morning and evening meals. Steady-state serum concentrations should not be anticipated before 11 days.

Infants and Children: Digitalization must be individualized. Divided daily dosing is recommended for infants and young children. In these patients, where dosage adjustment is frequent and outside the fixed dosages available, Lanoxicaps may not be the formulation of choice. Children over 10 years of age require adult dosages in proportion to their body weight.

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.

Lanoxin® Injection Pediatric can be used to achieve rapid digitalization, with conversion to an oral Lanoxin formulation for maintenance therapy. If patients are switched from IV to oral digoxin tablets or elixir, allowances must be made for differences in bioavailability when calculating maintenance dosages (see bioavailability table in CLINICAL PHARMACOLOGY section and dosing table below).

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Digitalizing and daily maintenance doses for each age group are given below and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger doses are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation.

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.

Usual Digitalizing and Maintenance Dosages for Lanoxicaps in
Children with Normal Renal Function Based on Lean Body Weight

Age	Digitalizing* Dose (µg/kg)	Daily† Maintenance Dose (µg/kg)
2-5 Years	25-35	25-35% of the oral or IV loading dose††
5-10 Years	15-30	
Over 10 Years	8-12	

*IV digitalizing doses are the same as Lanoxicaps digitalizing doses.

†Divided daily dosing is recommended for children under 10 years of age.

††Projected or actual digitalizing dose providing desired clinical response.

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More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon desired clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

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.

Serum Digoxin Concentrations: Measurement of serum digoxin concentrations can be helpful to the clinician in determining the state of digitalization and in assigning certain probabilities to the likelihood of digoxin intoxication. Studies in adults considered adequately digitalized (without evidence of atrial flutter and appear to tolerate higher levels than do patients with other indications. On the other hand, in adult patients with clinical evidence of digoxin toxicity, about two-thirds will have serum digoxin levels greater than 2.0 ng/ml. Thus, whereas levels less than 0.8 ng/ml are infrequently associated with toxicity, levels greater than 2.0 ng/ml are often associated with toxicity. Values in between are not very helpful in deciding whether a certain sign or symptom is more likely caused by digoxin toxicity or by something else. There are rare patients who are unable to tolerate digoxin even at serum concentrations below 0.8 ng/ml. Some researchers suggest that infants and young children tolerate slightly higher serum concentrations than do adults.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations for clinical use should be at least 6 to 8 hours after the last dose, regardless of the route of administration or formulation used. 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. After a single daily dose, the concentration will be 10 to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. Ideally, sampling for assessment of steady-state concentrations should be done just before the next 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 than digoxin.
4. Conditions (described in WARNINGS and PRECAUTIONS sections) causing an alteration in the sensitivity of the patient to digoxin.
5. The patient falls outside the norm in his response to or handling of digoxin. This decision should only be reached after exclusion of the other possibilities and generally should be confirmed by additional correlations of clinical observations with serum digoxin concentrations.

The serum concentration data should always be interpreted in the overall clinical context and an isolated serum concentration value should not be used alone as a basis for increasing or decreasing digoxin dosage.

Adjustment of Maintenance Dose in Previously Digitalized Patients: Lanoxicaps maintenance doses in individual patients on steady-state digoxin can be adjusted upward or downward in proportion to the ratio of the desired versus the measured serum concentration. For example, a patient at steady-state on 100 µg (0.1 mg) of Lanoxicaps per day with a measured serum concentration of 0.7 ng/ml, should have the dose increased to 200 µg (0.2 mg) per day to achieve a steady-state serum concentration of 1.4 ng/ml, assuming the serum digoxin concentration measurement is correct, renal function remains stable during this time and the needed adjustment is not the result of a problem with compliance.

Dosage Adjustment When Changing Preparations: The absolute bioavailability of the capsule formulation is greater than that of the standard tablets and very near that of the intravenous dosage form. As a result the doses recommended for Lanoxicaps capsules are the same as those for Lanoxin® injection (see CLINICAL PHARMACOLOGY section). Adjustments in dosage will seldom be necessary when converting a patient from intravenous to Lanoxicaps formulation. The differences in bioavailability between Lanoxin Injection or Lanoxicaps, and Lanoxin Elixir Pediatric or Lanoxin Tablets must be considered when changing patients from one dosage form to another.

Lanoxin Injection and Lanoxicaps doses of 100 µg (0.1 mg) and 200 µg (0.2 mg) are approximately equivalent to 125 µg (0.125 mg) and 250 µg (0.25 mg) doses of Lanoxin Tablets and Elixir Pediatric (see table in CLINICAL PHARMACOLOGY section). Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

HOW SUPPLIED:

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 50 µg (0.05 mg): bottles of 100, 1000 and Unit Dose Pack, box of 100. Imprint A2C (red)
LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 100 µg (0.10 mg): bottles of 100, 1000 and Unit Dose Pack, box of 100. Imprint B2C (yellow)
LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 200 µg (0.20 mg): bottles of 100, 1000 and Unit Dose Pack, box of 100. Imprint C2C (green)
Store at 15°-30°C (59°-86°F) in a dry place and protect from light.

Also Available:

LANOXIN® (DIGOXIN) TABLETS, Scored 125 µg (0.125 mg): Bottles of 100 and 1000; Unit Dose Pack of 1000; Unit of Use bottles of 30. Imprinted with LANOXIN and Y3B (yellow).

LANOXIN (DIGOXIN) TABLETS, Scored 250 µg (0.25 mg): Bottles of 100, 1000 and 5000; Unit Dose Pack of 100; Unit of Use bottles of 30 and 100. Imprinted with LANOXIN and X3A (white).

LANOXIN (DIGOXIN) TABLETS, Scored 500 µg (0.5 mg): Bottles of 100. Imprinted with LANOXIN and T9A (green).

LANOXIN (DIGOXIN) ELIXIR PEDIATRIC, 50 µg (0.05 mg) per ml: bottle of 60 ml with calibrated dropper.

LANOXIN (DIGOXIN) INJECTION, 500 µg (0.5 mg) in 2 ml (250 µg [0.25 mg] per ml); boxes of 12 and 100 ampuls.

LANOXIN (DIGOXIN) INJECTION PEDIATRIC, 100 µg (0.1 mg) in 1 ml; box of 50 ampuls.

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