

1 PRESCRIBING INFORMATION

2 **LANOXIN[®]**

3 **(digoxin)**

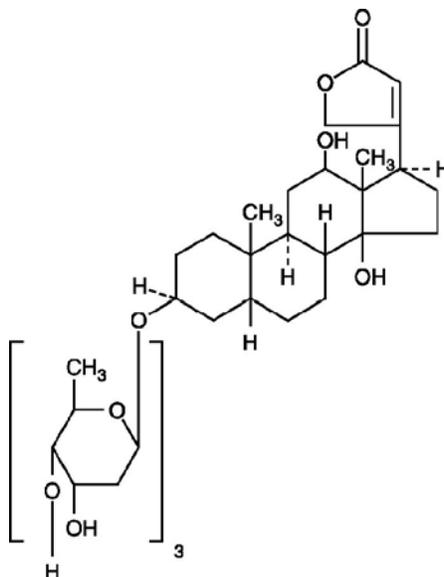
4 **Injection**

5 **500 mcg (0.5 mg) in 2 mL (250 mcg [0.25 mg] per mL)**

6 **DESCRIPTION**

7 LANOXIN (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of
8 drugs having in common specific effects on the myocardium. These drugs are found in a number
9 of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term “digitalis” is used to
10 designate the whole group of glycosides. The glycosides are composed of 2 portions: a sugar and
11 a cardenolide (hence “glycosides”).

12 Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D*-ribo-hexopyranosyl-
13 (1→4)-*O*-2,6-dideoxy-β-*D*-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-ribo-
14 hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is C₄₁H₆₄O₁₄,
15 its molecular weight is 780.95, and its structural formula is:



17
18
19 Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug
20 is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in
21 chloroform; and freely soluble in pyridine.

22 LANOXIN Injection is a sterile solution of digoxin for intravenous or intramuscular injection.
23 The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of
24 6.8 to 7.2 with 0.17% dibasic sodium phosphate and 0.08% anhydrous citric acid. Each 2-mL
25 ampul contains 500 mcg (0.5 mg) digoxin (250 mcg [0.25 mg] per mL). Dilution is not required.

26 **CLINICAL PHARMACOLOGY**

27 **Mechanism of Action:** Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates
28 the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase
29 in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium
30 exchange) an increase in the intracellular concentration of calcium. The beneficial effects of
31 digoxin result from direct actions on cardiac muscle, as well as indirect actions on the
32 cardiovascular system mediated by effects on the autonomic nervous system. The autonomic
33 effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the
34 sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in
35 increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and
36 renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic
37 consequences of these direct and indirect effects are: (1) an increase in the force and velocity of
38 myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of
39 activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal
40 deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through
41 the AV node (vagamimetic effect). The effects of digoxin in heart failure are mediated by its
42 positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in
43 atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases
44 sympathetic outflow from the central nervous system (CNS). This increase in sympathetic
45 activity may be an important factor in digitalis toxicity.

46 **Pharmacokinetics:** Note: the following data are from studies performed in adults, unless
47 otherwise stated.

48 **Absorption:** Comparisons of the systemic availability and equivalent doses for preparations
49 of LANOXIN are shown in Table 1.

50

51 **Table 1. Comparisons of the Systemic Availability and Equivalent Doses for Preparations**
52 **of LANOXIN**

Product	Absolute Bioavailability	Equivalent Doses (mcg) ^a Among Dosage Forms			
		62.5	125	250	500
LANOXIN Tablets	60 - 80%	62.5	125	250	500
LANOXIN Injection/IV	100%	50	100	200	400

53 ^a For example, 125 mcg LANOXIN Tablets equivalent to 100 mcg LANOXIN Injection/IV.

54

55 **Distribution:** Following drug administration, a 6- to 8-hour tissue distribution phase is
56 observed. This is followed by a much more gradual decline in the serum concentration of the
57 drug, which is dependent on the elimination of digoxin from the body. The peak height and slope
58 of the early portion (absorption/distribution phases) of the serum concentration-time curve are
59 dependent upon the route of administration and the absorption characteristics of the formulation.
60 Clinical evidence indicates that the early high serum concentrations do not reflect the
61 concentration of digoxin at its site of action, but that with chronic use, the steady-state

62 post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate
63 with pharmacologic effects. In individual patients, these post-distribution serum concentrations
64 may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND
65 ADMINISTRATION: Serum Digoxin Concentrations).

66 Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution.
67 Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin
68 concentration in the newborn is similar to the serum concentration in the mother. Approximately
69 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not
70 significantly altered by large changes in fat tissue weight, so that its distribution space correlates
71 best with lean (i.e., ideal) body weight, not total body weight.

72 **Metabolism:** Only a small percentage (16%) of a dose of digoxin is metabolized. The end
73 metabolites, which include 3 β -digoxigenin, 3-keto-digoxigenin, and their glucuronide and
74 sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation,
75 and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450
76 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

77 **Excretion:** Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin
78 eliminated at any time is proportional to the total body content). Following intravenous
79 administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the
80 urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely
81 independent of urine flow. In healthy volunteers with normal renal function, digoxin has a
82 half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin
83 is not effectively removed from the body by dialysis, exchange transfusion, or during
84 cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the
85 blood.

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

90 The clearance of digoxin can be primarily correlated with renal function as indicated by
91 creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance
92 includes age, body weight, and gender. Table 5 that provides the usual daily maintenance dose
93 requirements of LANOXIN Tablets based on creatinine clearance (per 70 kg) is presented in the
94 DOSAGE AND ADMINISTRATION section.

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

97 **Pharmacodynamic and Clinical Effects:** The times to onset of pharmacologic effect and to
98 peak effect of preparations of LANOXIN are shown in Table 2.

99

100 **Table 2. Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of**
 101 **LANOXIN**

Product	Time to Onset of Effect ^a	Time to Peak Effect ^a
LANOXIN Tablets	0.5 - 2 hours	2 - 6 hours
LANOXIN Injection/IV	5 - 30 minutes ^b	1 - 4 hours

102 ^a Documented for ventricular response rate in atrial fibrillation, inotropic effects and
 103 electrocardiographic changes.

104 ^b Depending upon rate of infusion.

105

106 **Hemodynamic Effects:** Digoxin produces hemodynamic improvement in patients with
 107 heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers
 108 pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular
 109 resistance. These hemodynamic effects are accompanied by an increase in the left ventricular
 110 ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

111 **Chronic Heart Failure:** Two 12-week, double-blind, placebo-controlled studies enrolled
 112 178 (RADIANCE trial) and 88 (PROVED trial) patients with NYHA class II or III heart failure
 113 previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and
 114 randomized them to placebo or treatment with LANOXIN Tablets. Both trials demonstrated
 115 better preservation of exercise capacity in patients randomized to LANOXIN. Continued
 116 treatment with LANOXIN reduced the risk of developing worsening heart failure, as evidenced
 117 by heart failure-related hospitalizations and emergency care and the need for concomitant heart
 118 failure therapy. The larger study also showed treatment-related benefits in NYHA class and
 119 patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

120 The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized,
 121 double-blind, placebo-controlled mortality study of 6,801 patients with heart failure and left
 122 ventricular ejection fraction ≤ 0.45 . At randomization, 67% were NYHA class I or II, 71% had
 123 heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving
 124 concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or
 125 LANOXIN Tablets, the dose of which was adjusted for the patient's age, sex, lean body weight,
 126 and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to
 127 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall
 128 all-cause mortality was 35% with no difference between groups (95% confidence limits for
 129 relative risk of 0.91 to 1.07). LANOXIN was associated with a 25% reduction in the number of
 130 hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least
 131 1 hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

132 Use of LANOXIN was associated with a trend to increase time to all-cause death or
 133 hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as
 134 more severe disease, as shown in Table 3. Although the effect on all-cause death or
 135 hospitalization was not statistically significant, much of the apparent benefit derived from effects
 136 on mortality and hospitalization attributed to heart failure.

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Table 3. Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization

	n	Risk of All-Cause Mortality or All-Cause Hospitalization ^a			Risk of HF-Related Mortality or HF-Related Hospitalization ^a		
		Placebo	LANOXIN	Relative risk ^b	Placebo	LANOXIN	Relative risk ^b
All patients (EF ≤0.45)	6,801	604	593	0.94 (0.88-1.00)	294	217	0.69 (0.63-0.76)
NYHA I/II	4,571	549	541	0.96 (0.89-1.04)	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4,543	568	571	0.99 (0.91-1.07)	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4,455	561	563	0.98 (0.91-1.06)	239	180	0.71 (0.63-0.81)
NYHA III/IV	2,224	719	696	0.88 (0.80-0.97)	402	295	0.65 (0.57-0.75)
EF <0.25	2,258	677	637	0.84 (0.76-0.93)	394	270	0.61 (0.53-0.71)
CTR >0.55	2,346	687	650	0.85 (0.77-0.94)	398	287	0.65 (0.57-0.75)
EF >0.45 ^c	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

140 ^a Number of patients with an event during the first 2 years per 1,000 randomized patients.

141 ^b Relative risk (95% confidence interval).

142 ^c DIG Ancillary Study.

143

144 In situations where there is no statistically significant benefit of treatment evident from a
145 trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted
146 cautiously.

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

150 **INDICATIONS AND USAGE**

151 **Heart Failure:** LANOXIN is indicated for the treatment of mild to moderate heart failure.

152 LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as
153 evidenced by exercise capacity and heart failure-related hospitalizations and emergency care,
154 while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic
155 and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these 3 drugs
156 cannot be specified.

157 **Atrial Fibrillation:** LANOXIN is indicated for the control of ventricular response rate in
158 patients with chronic atrial fibrillation.

159 **CONTRAINDICATIONS**

160 Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients
161 with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis
162 preparations usually constitutes a contraindication to digoxin.

163 **WARNINGS**

164 **Sinus Node Disease and AV Block:** Because digoxin slows sinoatrial and AV conduction,
165 the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or
166 sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or
167 complete heart block in patients with pre-existing incomplete AV block. In such patients
168 consideration should be given to the insertion of a pacemaker before treatment with digoxin.

169 **Accessory AV Pathway (Wolff-Parkinson-White Syndrome):** After intravenous digoxin
170 therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory
171 AV pathway have developed increased antegrade conduction across the accessory pathway
172 bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation.
173 Unless conduction down the accessory pathway has been blocked (either pharmacologically or
174 by surgery), digoxin should not be used in such patients. The treatment of paroxysmal
175 supraventricular tachycardia in such patients is usually direct-current cardioversion.

176 **Use in Patients With Preserved Left Ventricular Systolic Function:** Patients with
177 certain disorders involving heart failure associated with preserved left ventricular ejection
178 fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive
179 cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale.
180 Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow
181 obstruction due to the inotropic effects of digoxin. Digoxin should generally be avoided in these
182 patients, although it has been used for ventricular rate control in the subgroup of patients with
183 atrial fibrillation.

184 **PRECAUTIONS**

185 **Use in Patients With Impaired Renal Function:** Digoxin is primarily excreted by the
186 kidneys; therefore, patients with impaired renal function require smaller than usual maintenance
187 doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged
188 elimination half-life, a longer period of time is required to achieve an initial or new steady-state
189 serum concentration in patients with renal impairment than in patients with normal renal
190 function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high
191 risk for toxicity, and toxic effects will last longer in such patients than in patients with normal
192 renal function.

193 **Use in Patients With Electrolyte Disorders:** In patients with hypokalemia or
194 hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL,

195 because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is
196 desirable to maintain normal serum potassium and magnesium concentrations in patients being
197 treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or
198 prolonged vomiting, as well as the use of the following drugs or procedures: diuretics,
199 amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal
200 secretions.

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

207 **Use in Thyroid Disorders and Hypermetabolic States:** Hypothyroidism may reduce the
208 requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic
209 or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated
210 by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states
211 are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is
212 used.

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

216 **Use During Electrical Cardioversion:** It may be desirable to reduce the dose of digoxin for
217 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of
218 ventricular arrhythmias, but physicians must consider the consequences of increasing the
219 ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective
220 cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible
221 energy level should be selected to avoid provoking ventricular arrhythmias.

222 **Use in Patients With Myocarditis:** Digoxin can rarely precipitate vasoconstriction and
223 therefore should be avoided in patients with myocarditis.

224 **Use in Patients With Beri Beri Heart Disease:** Patients with beri beri heart disease may
225 fail to respond adequately to digoxin if the underlying thiamine deficiency is not treated
226 concomitantly.

227 **Laboratory Test Monitoring:** Patients receiving digoxin should have their serum electrolytes
228 and renal function (serum creatinine concentrations) assessed periodically; the frequency of
229 assessments will depend on the clinical setting. For discussion of serum digoxin concentrations,
230 see DOSAGE AND ADMINISTRATION.

231 **Drug Interactions:** Potassium-depleting *diuretics* are a major contributing factor to digitalis
232 toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce
233 serious arrhythmias in digitalized patients. *Quinidine*, *verapamil*, *amiodarone*, *propafenone*,
234 *indomethacin*, *itraconazole*, *alprazolam*, and *spironolactone* raise the serum digoxin

235 concentration due to a reduction in clearance and/or in volume of distribution of the drug, with
236 the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and
237 possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in
238 patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis
239 intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may
240 increase digoxin absorption. *Antacids*, *kaolin-pectin*, *sulfasalazine*, *neomycin*, *cholestyramine*,
241 certain *anticancer drugs*, and *metoclopramide* may interfere with intestinal digoxin absorption,
242 resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin
243 concentration, especially in patients with renal dysfunction, by increasing the non-renal
244 clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs
245 (e.g., *quinine*, *penicillamine*) on serum digoxin concentration. *Thyroid* administration to a
246 digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use
247 of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may
248 cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in
249 digitalized patients. Although calcium channel blockers and digoxin may be useful in
250 combination to control atrial fibrillation, their additive effects on AV node conduction can result
251 in advanced or complete heart block. Both digitalis glycosides and beta-blockers slow
252 atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of
253 bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol
254 are administered concomitantly. Therefore, increased monitoring of digoxin is recommended
255 when initiating, adjusting, or discontinuing carvedilol.

256 Due to the considerable variability of these interactions, the dosage of digoxin should be
257 individualized when patients receive these medications concurrently. Furthermore, caution
258 should be exercised when combining digoxin with any drug that may cause a significant
259 deterioration in renal function, since a decline in glomerular filtration or tubular secretion may
260 impair the excretion of digoxin.

261 **Drug/Laboratory Test Interactions:** The use of therapeutic doses of digoxin may cause
262 prolongation of the PR interval and depression of the ST segment on the electrocardiogram.
263 Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise
264 testing. These electrophysiologic effects reflect an expected effect of the drug and are not
265 indicative of toxicity.

266 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Digoxin showed no genotoxic
267 potential in *in vitro* studies (Ames test and mouse lymphoma). No data are available on the
268 carcinogenic potential of digoxin, nor have studies been conducted to assess its potential to affect
269 fertility.

270 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Animal reproduction studies have
271 not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm
272 when administered to a pregnant woman or can affect reproductive capacity. Digoxin should be
273 given to a pregnant woman only if clearly needed.

274 **Nursing Mothers:** Studies have shown that digoxin concentrations in the mother's serum and
275 milk are similar. However, the estimated exposure of a nursing infant to digoxin via
276 breastfeeding will be far below the usual infant maintenance dose. Therefore, this amount should
277 have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when
278 digoxin is administered to a nursing woman.

279 **Pediatric Use:** Newborn infants display considerable variability in their tolerance to digoxin.
280 Premature and immature infants are particularly sensitive to the effects of digoxin, and the
281 dosage of the drug must not only be reduced but must be individualized according to their degree
282 of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

283 **Geriatric Use:** The majority of clinical experience gained with digoxin has been in the elderly
284 population. This experience has not identified differences in response or adverse effects between
285 the elderly and younger patients. However, this drug is known to be substantially excreted by the
286 kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal
287 function. Because elderly patients are more likely to have decreased renal function, care should
288 be taken in dose selection, which should be based on renal function, and it may be useful to
289 monitor renal function (see DOSAGE AND ADMINISTRATION).

290 **ADVERSE REACTIONS**

291 In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than
292 those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when
293 digoxin is used within the recommended dose range or therapeutic serum concentration range
294 and when there is careful attention to concurrent medications and conditions.

295 Because some patients may be particularly susceptible to side effects with digoxin, the dosage
296 of the drug should always be selected carefully and adjusted as the clinical condition of the
297 patient warrants. In the past, when high doses of digoxin were used and little attention was paid
298 to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and
299 severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for
300 about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.
301 However, available evidence suggests that the incidence and severity of digoxin toxicity has
302 decreased substantially in recent years. In recent controlled clinical trials, in patients with
303 predominantly mild to moderate heart failure, the incidence of adverse experiences was
304 comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the
305 incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking LANOXIN
306 Tablets compared to 0.9% in patients taking placebo. In this trial, the most common
307 manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS
308 manifestations were less common.

309 **Adults: Cardiac:** Therapeutic doses of digoxin may cause heart block in patients with pre-
310 existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose
311 of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block
312 is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances,

313 such as first-degree, second-degree (Wenckebach), or third-degree heart block (including
 314 asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm;
 315 unifocal or multifocal premature contractions (especially bigeminy or trigeminy);
 316 ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST
 317 segment depression which should not by themselves be considered digoxin toxicity. Cardiac
 318 toxicity can also occur at therapeutic doses in patients who have conditions which may alter their
 319 sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

320 **Gastrointestinal:** Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the
 321 use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic
 322 necrosis of the intestines.

323 **CNS:** Digoxin can produce visual disturbances (blurred or yellow vision), headache,
 324 weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression,
 325 delirium, and hallucination).

326 **Other:** Gynecomastia has been occasionally observed following the prolonged use of
 327 digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely
 328 observed.

329 Table 4 summarizes the incidence of those adverse experiences listed above for patients
 330 treated with LANOXIN Tablets or placebo from 2 randomized, double-blind, placebo-controlled
 331 withdrawal trials. Patients in these trials were also receiving diuretics with or without
 332 angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were
 333 randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients
 334 following dosage titration with the use of serum digoxin concentrations and careful follow-up.
 335 These adverse experiences are consistent with results from a large, placebo-controlled mortality
 336 trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

337
 338 **Table 4. Adverse Experiences In 2 Parallel, Double-Blind, Placebo-Controlled Withdrawal**
 339 **Trials (Number of Patients Reporting)**

Adverse Experience	Digoxin Patients (n = 123)	Placebo Patients (n = 125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6

CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

340

341 **Infants and Children:** The side effects of digoxin in infants and children differ from those
342 seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting,
343 diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of
344 overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with
345 digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus
346 bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are
347 conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or
348 without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common.
349 Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in
350 the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that
351 develops in a child taking digoxin should be assumed to be caused by digoxin, until further
352 evaluation proves otherwise.

353 **OVERDOSAGE**

354 **Signs and Symptoms:** The signs and symptoms of toxicity are generally similar to those
355 described in the ADVERSE REACTIONS section but may be more frequent and can be more
356 severe. Signs and symptoms of digoxin toxicity become more frequent with levels above
357 2 ng/mL. However, in deciding whether a patient's symptoms are due to digoxin, the clinical
358 state together with serum electrolyte levels and thyroid function are important factors (see
359 DOSAGE AND ADMINISTRATION).

360 **Adults:** In adults without heart disease, clinical observation suggests that an overdose of
361 digoxin of 10 to 15 mg was the dose resulting in death of half of the patients. If more than 25 mg
362 of digoxin was ingested by an adult without heart disease, death or progressive toxicity
363 responsive only to digoxin-binding Fab antibody fragments resulted. Cardiac manifestations are
364 the most frequent and serious sign of both acute and chronic toxicity. Peak cardiac effects
365 generally occur 3 to 6 hours following overdosage and may persist for the ensuing 24 hours or
366 longer. Digoxin toxicity may result in almost any type of arrhythmia (see ADVERSE
367 REACTIONS). Multiple rhythm disturbances in the same patient are common. Cardiac arrest
368 from asystole or ventricular fibrillation due to digoxin toxicity is usually fatal.

369 Among the extra-cardiac manifestations, gastrointestinal symptoms (e.g. nausea, vomiting,
370 anorexia) are very common (up to 80% incidence) and precede cardiac manifestations in
371 approximately half of the patients in most literature reports. Neurologic manifestations (e.g.

372 dizziness, various CNS disturbances), fatigue, and malaise are very common. Visual
373 manifestations may also occur with aberration in color vision (predominance of yellow green)
374 the most frequent. Neurological and visual symptoms may persist after other signs of toxicity
375 have resolved. In chronic toxicity, non-specific extra-cardiac symptoms, such as malaise and
376 weakness, may predominate.

377 **Children:** In children aged 1 to 3 years without heart disease, clinical observation suggests
378 that an overdose of digoxin of 6 to 10 mg was the dose resulting in death in half of the patients.
379 If more than 10 mg of digoxin was ingested by a child aged 1 to 3 years without heart disease,
380 the outcome was uniformly fatal when Fab fragment treatment was not given. Most
381 manifestations of toxicity in children occur during or shortly after the loading phase with
382 digoxin. The same arrhythmias or combination of arrhythmias that occur in adults can occur in
383 pediatrics. Sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen
384 less frequently in the pediatric population. Pediatric patients are more likely to present with an
385 AV conduction disturbance or a sinus bradycardia. Any arrhythmia or alteration in cardiac
386 conduction that develops in a child taking digoxin should be assumed to be caused by digoxin,
387 until further evaluation proves otherwise.

388 The frequent extracardiac manifestations similar to those seen in adults are gastrointestinal,
389 CNS, and visual. However, nausea and vomiting are not frequent in infants and small children.

390 In addition to the undesirable effects seen with recommended doses, weight loss in older age
391 groups and failure to thrive in infants, abdominal pain due to mesenteric artery ischemia,
392 drowsiness, and behavioral disturbances including psychotic manifestations have been reported
393 in overdose.

394 **Treatment:** In addition to cardiac monitoring, digoxin should be temporarily discontinued until
395 the adverse reaction resolves and may be all that is required to treat the adverse reaction such as
396 in asymptomatic bradycardia or digoxin-related heart block. Every effort should also be made to
397 correct factors that may contribute to the adverse reaction (such as electrolyte disturbances,
398 thyroid function, or concurrent medications) (see WARNINGS and PRECAUTIONS: Drug
399 Interactions). Once the adverse reaction has resolved, therapy with digoxin may be reinstated,
400 following a careful reassessment of dose.

401 When the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional
402 therapy may be needed.

403 If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration
404 should be given to the reversal of toxicity with Digoxin Immune Fab (Ovine) [DIGIBIND[®] or
405 DIGIFAB[®]] (see Massive Digitalis Overdosage subsection), the use of atropine, or the insertion
406 of a temporary cardiac pacemaker. Digoxin Immune Fab (Ovine) is a specific antidote for
407 digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to
408 digoxin overdosage.

409 If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the
410 correction of electrolyte disorders, particularly if hypokalemia (see Administration of Potassium

411 subsection) or hypomagnesemia is present. Ventricular arrhythmias may respond to lidocaine or
412 phenytoin.

413 **Administration of Potassium:** Before administering potassium in digoxin overdose for
414 hypokalemia, the serum potassium must be known and every effort should be made to maintain
415 the serum potassium concentration between 4 and 5.5 mmol/L. Potassium salts should be
416 avoided as they may be dangerous in patients who manifest bradycardia or heart block due to
417 digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive
418 digitalis overdosage. Potassium is usually administered orally, but when correction of the
419 arrhythmia is urgent and the serum potassium concentration is low, potassium may be
420 administered cautiously by the intravenous route. The electrocardiogram should be monitored for
421 any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the
422 arrhythmia.

423 **Massive Digitalis Overdosage:** Manifestations of life-threatening toxicity include
424 ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart
425 block.

426 Digoxin Immune Fab (Ovine) should be used to reverse the toxic effects of ingestion of a
427 massive overdose. The decision to administer Digoxin Immune Fab (Ovine) to a patient who has
428 ingested a massive dose of digoxin but who has not yet manifested life-threatening toxicity
429 should depend on the likelihood that life-threatening toxicity will occur (see above).

430 Digoxin is not effectively removed from the body by dialysis due to its large extravascular
431 volume of distribution. Patients with massive digitalis ingestion should receive large doses of
432 activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric
433 recirculation. Emesis may be indicated especially if ingestion has occurred within 30 minutes of
434 the patient's presentation at the hospital. Emesis should not be induced in patients who are
435 obtunded. If a patient presents more than 2 hours after ingestion or already has toxic
436 manifestations, it may be unsafe to induce vomiting because such maneuvers may induce an
437 acute vagal episode that can worsen digitalis-related arrhythmias.

438 In cases where a large amount of digoxin has been ingested, hyperkalemia may be present due
439 to release of potassium from skeletal muscle. Hyperkalemia caused by massive digitalis toxicity
440 is best treated with Digoxin Immune Fab (Ovine); initial treatment with glucose and insulin may
441 also be required if hyperkalemia itself is acutely life-threatening.

442 **DOSAGE AND ADMINISTRATION**

443 **General:** Recommended dosages of digoxin may require considerable modification because of
444 individual sensitivity of the patient to the drug, the presence of associated conditions, or the use
445 of concurrent medications.

446 Parenteral administration of digoxin should be used only when the need for rapid
447 digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead
448 to severe pain at the injection site, thus intravenous administration is preferred. If the drug must

449 be administered by the intramuscular route, it should be injected deep into the muscle followed
450 by massage. No more than 500 mcg (2 mL) should be injected into a single site.

451 LANOXIN Injection can be administered undiluted or diluted with a 4-fold or greater volume
452 of Sterile Water for Injection, 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. The
453 use of less than a 4-fold volume of diluent could lead to precipitation of the digoxin. Immediate
454 use of the diluted product is recommended.

455 If tuberculin syringes are used to measure very small doses, one must be aware of the problem
456 of inadvertent overadministration of digoxin. The syringe should *not* be flushed with the
457 parenteral solution after its contents are expelled into an indwelling vascular catheter.

458 Slow infusion of LANOXIN Injection is preferable to bolus administration. Rapid infusion of
459 digitalis glycosides has been shown to cause systemic and coronary arteriolar constriction, which
460 may be clinically undesirable. Caution is thus advised and LANOXIN Injection should probably
461 be administered over a period of 5 minutes or longer. Mixing of LANOXIN Injection with other
462 drugs in the same container or simultaneous administration in the same intravenous line is not
463 recommended.

464 In selecting a dose of digoxin, the following factors must be considered:

- 465 1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body
466 weight.
- 467 2. The patient's renal function, preferably evaluated on the basis of estimated creatinine
468 clearance.
- 469 3. The patient's age. Infants and children require different doses of digoxin than adults. Also,
470 advanced age may be indicative of diminished renal function even in patients with normal
471 serum creatinine concentration (i.e., below 1.5 mg/dL).
- 472 4. Concomitant disease states, concurrent medications, or other factors likely to alter the
473 pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

474 **Serum Digoxin Concentrations:** In general, the dose of digoxin used should be determined
475 on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to
476 the clinician in determining the adequacy of digoxin therapy and in assigning certain
477 probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered
478 adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging
479 from 0.8 to 2.0 ng/mL (lower serum trough concentrations of 0.5 to 1 ng/mL may be appropriate
480 in some adult patients, see Maintenance Dosing). However, digoxin may produce clinical
481 benefits even at serum concentrations below this range. About two-thirds of adult patients with
482 clinical toxicity have serum digoxin concentrations greater than 2.0 ng/mL. However, since one-
483 third of patients with clinical toxicity have concentrations less than 2.0 ng/mL, values below
484 2.0 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin
485 therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations
486 below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be
487 interpreted in the overall clinical context, and an isolated measurement should not be used alone
488 as the basis for increasing or decreasing the dose of the drug.

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

497 If a discrepancy exists between the reported serum concentration and the observed clinical
498 response, the clinician should consider the following possibilities:

- 499 1. Analytical problems in the assay procedure.
- 500 2. Inappropriate serum sampling time.
- 501 3. Administration of a digitalis glycoside other than digoxin.
- 502 4. Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the
503 sensitivity of the patient to digoxin.
- 504 5. Serum digoxin concentration may decrease acutely during periods of exercise without any
505 associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

506 **Heart Failure: Adults:** Digitalization may be accomplished by either of 2 general approaches
507 that vary in dosage and frequency of administration, but reach the same endpoint in terms of total
508 amount of digoxin accumulated in the body.

- 509 1. If rapid digitalization is considered medically appropriate, it may be achieved by
510 administering a loading dose based upon projected peak digoxin body stores. Maintenance
511 dose can be calculated as a percentage of the loading dose.
- 512 2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose,
513 thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin
514 concentrations will be achieved in approximately 5 half-lives of the drug for the individual
515 patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

516 **Rapid Digitalization With a Loading Dose:** LANOXIN Injection is frequently used
517 to achieve rapid digitalization, with conversion to LANOXIN Tablets for maintenance therapy. If
518 patients are switched from intravenous to oral digoxin formulations, allowances must be made
519 for differences in bioavailability when calculating maintenance dosages (see Table 1, CLINICAL
520 PHARMACOLOGY: Pharmacokinetics and dosing Table 5).

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

523 Peak digoxin body stores of 8 to 12 mcg/kg should provide therapeutic effect with minimum
524 risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered
525 digoxin distribution and elimination, projected peak body stores for patients with renal
526 insufficiency should be conservative (i.e., 6 to 10 mcg/kg) (see PRECAUTIONS).

527 The loading dose should be administered in several portions, with roughly half the total given
528 as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour

529 intervals, **with careful assessment of clinical response before each additional dose.** If the
 530 patient's clinical response necessitates a change from the calculated loading dose of digoxin,
 531 then calculation of the maintenance dose should be based upon the amount actually given.

532 A single initial intravenous dose of 400 to 600 mcg (0.4 to 0.6 mg) of LANOXIN Injection
 533 usually produces a detectable effect in 5 to 30 minutes that becomes maximal in 1 to 4 hours.
 534 Additional doses of 100 to 300 mcg (0.1 to 0.3 mg) may be given cautiously at 6- to 8-hour
 535 intervals until clinical evidence of an adequate effect is noted. The usual amount of LANOXIN
 536 Injection that a 70-kg patient requires to achieve 8- to 12-mcg/kg peak body stores is 600 to
 537 1,000 mcg (0.6 to 1.0 mg).

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

546 In a subset of approximately 1,800 patients enrolled in the DIG trial (wherein dosing was
 547 based on an algorithm similar to that in Table 5) the mean (\pm SD) serum digoxin concentrations
 548 at 1 month and 12 months were 1.01 ± 0.47 ng/mL and 0.97 ± 0.43 ng/mL, respectively. There
 549 are no rigid guidelines as to the range of serum concentrations that are most efficacious. Several
 550 post hoc analyses of heart failure patients in the DIG trial suggest that the optimal trough digoxin
 551 serum level may be 0.5 ng/mL to 1 ng/mL.

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

554 Maintenance Dose = Peak Body Stores (i.e., Loading Dose) x % Daily Loss/100

555 Where: % Daily Loss = $14 + Ccr/5$

556 (Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m² body surface area.)

557 Table 5 provides average daily maintenance dose requirements of LANOXIN Injection for
 558 patients with heart failure based upon lean body weight and renal function:

560 **Table 5. Usual Daily Maintenance Dose Requirements (mcg) of LANOXIN Injection for**
 561 **Estimated Peak Body Stores of 10 mcg/kg^a**

Corrected Ccr (mL/min per 70 kg) ^b	Lean Body Weight							Number of Days Before Steady State Achieved ^c
	kg	50	60	70	80	90	100	
	lb	110	132	154	176	198	220	
0		75 ^d	75	100	100	125	150	22
10		75	100	100	125	150	150	19
20		100	100	125	150	150	175	16
30		100	125	150	150	175	200	14

40	100	125	150	175	200	225	13
50	125	150	175	200	225	250	12
60	125	150	175	200	225	250	11
70	150	175	200	225	250	275	10
80	150	175	200	250	275	300	9
90	150	200	225	250	300	325	8
100	175	200	250	275	300	350	7

562 ^a Daily maintenance doses have been rounded to the nearest 25-mcg increment.

563 ^b Ccr is creatinine clearance, corrected to 70-kg body weight or 1.73 m² body surface area. *For*
564 *adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg
565 body weight) may be estimated in men as (140 - Age)/Scr. For women, this result should be
566 multiplied by 0.85. *Note: This equation cannot be used for estimating creatinine clearance in*
567 *infants or children.*

568 ^c If no loading dose administered.

569 ^d 75 mcg = 0.075 mg.

570

571 **Example:** Based on the above table, a patient in heart failure with an estimated lean body weight
572 of 70 kg and a Ccr of 60 mL/min should be given a dose of 175 mcg (0.175 mg) daily of
573 LANOXIN Injection. If no loading dose is administered, steady-state serum concentrations in
574 this patient should be anticipated at approximately 11 days.

575 **Infants and Children:** See the full prescribing information for LANOXIN Injection
576 Pediatric for specific recommendations.

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

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

586 **Dosage Adjustment When Changing Preparations:** The difference in bioavailability
587 between LANOXIN Injection or LANOXIN Tablets must be considered when changing patients
588 from one dosage form to the other.

589 HOW SUPPLIED

590 LANOXIN (digoxin) Injection, 500 mcg (0.5 mg) in 2 mL (250 mcg [0.25 mg] per mL); Boxes
591 of 10 (NDC 0173-0260-10) and 50 ampuls (NDC 0173-0260-35).

592 **Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP**
593 **Controlled Room Temperature] and protect from light.**

594
595 LANOXIN and DIGIBIND are registered trademarks of GlaxoSmithKline
596 DIGIFAB is a registered trademark of Prostherics Inc.
597



598
599 Manufactured by
600 Draxis Pharma Inc.
601 Kirkland, Canada H9H 4J4 for
602 GlaxoSmithKline
603 Research Triangle Park, NC 27709
604
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606
607 November 2011
608 LNJ:XPI

PRESCRIBING INFORMATION

LANOXIN[®]

(digoxin)

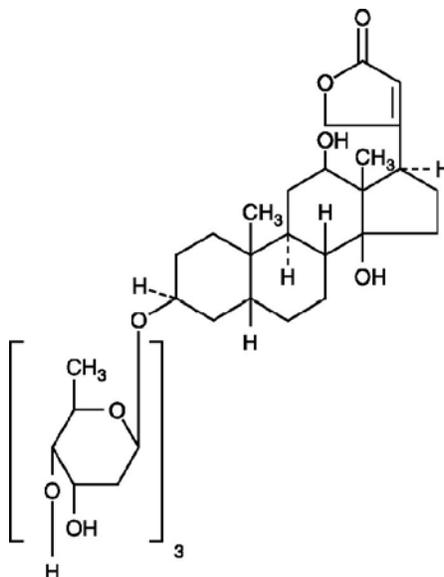
Injection Pediatric

100 mcg (0.1 mg) in 1 mL

DESCRIPTION

LANOXIN (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 of glycosides. The glycosides are composed of 2 portions: a sugar and a cardenolide (hence “glycosides”).

Digoxin is described chemically as (3 β ,5 β ,12 β)-3-[(*O*-2,6-dideoxy- β -*D*-ribo-hexopyranosyl-(1 \rightarrow 4)-*O*-2,6-dideoxy- β -*D*-ribo-hexopyranosyl-(1 \rightarrow 4)-2,6-dideoxy- β -*D*-ribo-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is C₄₁H₆₄O₁₄, its molecular weight is 780.95, and its structural formula is:



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.

LANOXIN Injection Pediatric is a sterile solution of digoxin for intravenous or intramuscular injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% sodium phosphate and 0.08% anhydrous citric acid. Each 1-mL ampul contains 100 mcg (0.1 mg) digoxin. Dilution is not required.

26 **CLINICAL PHARMACOLOGY**

27 **Mechanism of Action:** Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates
28 the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase
29 in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium
30 exchange) an increase in the intracellular concentration of calcium. The beneficial effects of
31 digoxin result from direct actions on cardiac muscle, as well as indirect actions on the
32 cardiovascular system mediated by effects on the autonomic nervous system. The autonomic
33 effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the
34 sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in
35 increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and
36 renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic
37 consequences of these direct and indirect effects are: (1) an increase in the force and velocity of
38 myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of
39 activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal
40 deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through
41 the AV node (vagamimetic effect). The effects of digoxin in heart failure are mediated by its
42 positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in
43 atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases
44 sympathetic outflow from the central nervous system (CNS). This increase in sympathetic
45 activity may be an important factor in digitalis toxicity.

46 **Pharmacokinetics:** Note: The following data are from studies performed in adults, unless
47 otherwise stated.

48 **Absorption:** Comparisons of the systemic availability and equivalent doses for preparations
49 of digoxin are shown in Table 1.

50

51 **Table 1. Comparisons of the Systemic Availability and Equivalent Doses for Preparations**
52 **of LANOXIN**

Product	Absolute Bioavailability	Equivalent Doses (mcg) ^a Among Dosage Forms			
		62.5	125	250	500
LANOXIN Tablets	60 - 80%	62.5	125	250	500
LANOXIN Injection/IV	100%	50	100	200	400

53 ^a For example, 125-mcg LANOXIN Tablets equivalent to 100 mcg LANOXIN Injection/IV.
54

55

56 **Distribution:** Following drug administration, a 6- to 8-hour tissue distribution phase is
57 observed. This is followed by a much more gradual decline in the serum concentration of the
58 drug, which is dependent on the elimination of digoxin from the body. The peak height and slope
59 of the early portion (absorption/distribution phases) of the serum concentration-time curve are
60 dependent upon the route of administration and the absorption characteristics of the formulation.
61 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

62 post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate
63 with pharmacologic effects. In individual patients, these post-distribution serum concentrations
64 may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND
65 ADMINISTRATION: Serum Digoxin Concentrations).

66 Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution.
67 Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin
68 concentration in the newborn is similar to the serum concentration in the mother. Approximately
69 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not
70 significantly altered by large changes in fat tissue weight, so that its distribution space correlates
71 best with lean (i.e., ideal) body weight, not total body weight.

72 **Metabolism:** Only a small percentage (16%) of a dose of digoxin is metabolized. The end
73 metabolites, which include 3 β -digoxigenin, 3-keto-digoxigenin, and their glucuronide and
74 sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation,
75 and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450
76 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

77 **Excretion:** Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin
78 eliminated at any time is proportional to the total body content). Following intravenous
79 administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the
80 urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely
81 independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-
82 life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is
83 not effectively removed from the body by dialysis, exchange transfusion, or during
84 cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the
85 blood.

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

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

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

95 **Pharmacodynamic and Clinical Effects:** The times to onset of pharmacologic effect and to
96 peak effect of preparations of LANOXIN are shown in Table 2.

97
98 **Table 2. Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of**
99 **LANOXIN**

Product	Time to Onset of Effect ^a	Time to Peak Effect ^a
LANOXIN Tablets	0.5 - 2 hours	2 - 6 hours

LANOXIN Injection/IV	5 - 30 minutes ^b	1 - 4 hours
----------------------	-----------------------------	-------------

100 ^a Documented for ventricular response rate in atrial fibrillation, inotropic effects and
101 electrocardiographic changes.

102 ^b Depending upon rate of infusion.

103

104 **Hemodynamic Effects:** Digoxin produces hemodynamic improvement in patients with
105 heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers
106 pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular
107 resistance. These hemodynamic effects are accompanied by an increase in the left ventricular
108 ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

109 **Chronic Heart Failure:** Two 12-week, double-blind, placebo-controlled studies enrolled
110 178 (RADIANCE trial) and 88 (PROVED trial) adult patients with NYHA class II or III heart
111 failure previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only)
112 and randomized them to placebo or treatment with LANOXIN Tablets. Both trials demonstrated
113 better preservation of exercise capacity in patients randomized to LANOXIN. Continued
114 treatment with LANOXIN reduced the risk of developing worsening heart failure, as evidenced
115 by heart failure-related hospitalizations and emergency care and the need for concomitant heart
116 failure therapy. The larger study also showed treatment-related benefits in NYHA class and
117 patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

118 The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-
119 blind, placebo-controlled mortality study of 6,801 adult patients with heart failure and left
120 ventricular ejection fraction ≤ 0.45 . At randomization, 67% were NYHA class I or II, 71% had
121 heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving
122 concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or
123 LANOXIN Tablets, the dose of which was adjusted for the patient's age, sex, lean body weight,
124 and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to
125 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-
126 cause mortality was 35% with no difference between groups (95% confidence limits for relative
127 risk of 0.91 to 1.07). LANOXIN was associated with a 25% reduction in the number of
128 hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least
129 1 hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

130 Use of LANOXIN was associated with a trend to increase time to all-cause death or
131 hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as
132 more severe disease, as shown in Table 3. Although the effect on all-cause death or
133 hospitalization was not statistically significant, much of the apparent benefit derived from effects
134 on mortality and hospitalization attributed to heart failure.

135

136 **Table 3. Subgroup Analyses of Mortality and Hospitalization During the First 2 Years**
 137 **Following Randomization**

	n	Risk of All-Cause Mortality or All-Cause Hospitalization ^a			Risk of HF-Related Mortality or HF-Related Hospitalization ^a		
		Placebo	LANOXIN	Relative risk ^b	Placebo	LANOXIN	Relative risk ^b
All patients (EF ≤0.45)	6,801	604	593	0.94 (0.88-1.00)	294	217	0.69 (0.63-0.76)
NYHA I/II	4,571	549	541	0.96 (0.89-1.04)	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4,543	568	571	0.99 (0.91-1.07)	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4,455	561	563	0.98 (0.91-1.06)	239	180	0.71 (0.63-0.81)
NYHA III/IV	2,224	719	696	0.88 (0.80-0.97)	402	295	0.65 (0.57-0.75)
EF <0.25	2,258	677	637	0.84 (0.76-0.93)	394	270	0.61 (0.53-0.71)
CTR >0.55	2,346	687	650	0.85 (0.77-0.94)	398	287	0.65 (0.57-0.75)
EF >0.45 ^c	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

138 ^a Number of patients with an event during the first 2 years per 1,000 randomized patients.

139 ^b Relative risk (95% confidence interval).

140 ^c DIG Ancillary Study.

141

142 In situations where there is no statistically significant benefit of treatment evident from a
 143 trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted
 144 cautiously.

145 **Chronic Atrial Fibrillation:** In adult patients with chronic atrial fibrillation, digoxin slows
 146 rapid ventricular response rate in a linear dose-response fashion from 0.25 to 0.75 mg/day.

147 Digoxin should not be used for the treatment of multifocal atrial tachycardia.

148 **INDICATIONS AND USAGE**

149 **Heart Failure:** LANOXIN is indicated for the treatment of mild to moderate heart failure.

150 LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as
 151 evidenced by exercise capacity and heart failure-related hospitalizations and emergency care,
 152 while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic
 153 and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these 3 drugs
 154 cannot be specified.

155 **Atrial Fibrillation:** LANOXIN is indicated for the control of ventricular response rate in
156 patients with chronic atrial fibrillation.

157 **CONTRAINDICATIONS**

158 Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients
159 with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis
160 preparations usually constitutes a contraindication to digoxin.

161 **WARNINGS**

162 **Sinus Node Disease and AV Block:** Because digoxin slows sinoatrial and AV conduction,
163 the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or
164 sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or
165 complete heart block in patients with pre-existing incomplete AV block. In such patients
166 consideration should be given to the insertion of a pacemaker before treatment with digoxin.

167 **Accessory AV Pathway (Wolff-Parkinson-White Syndrome):** After intravenous digoxin
168 therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory
169 AV pathway have developed increased antegrade conduction across the accessory pathway
170 bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation.
171 Unless conduction down the accessory pathway has been blocked (either pharmacologically or
172 by surgery), digoxin should not be used in such patients. The treatment of paroxysmal
173 supraventricular tachycardia in such patients is usually direct-current cardioversion.

174 **Use in Patients With Preserved Left Ventricular Systolic Function:** Patients with
175 certain disorders involving heart failure associated with preserved left ventricular ejection
176 fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive
177 cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale.
178 Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow
179 obstruction due to the inotropic effects of digoxin. Digoxin should generally be avoided in these
180 patients, although it has been used for ventricular rate control in the subgroup of patients with
181 atrial fibrillation.

182 **PRECAUTIONS**

183 **Use in Patients With Impaired Renal Function:** Digoxin is primarily excreted by the
184 kidneys; therefore, patients with impaired renal function require smaller than usual maintenance
185 doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged
186 elimination half-life, a longer period of time is required to achieve an initial or new steady-state
187 serum concentration in patients with renal impairment than in patients with normal renal
188 function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high
189 risk for toxicity, and toxic effects will last longer in such patients than in patients with normal
190 renal function.

191 **Use in Patients With Electrolyte Disorders:** In patients with hypokalemia or
192 hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL,

193 because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is
194 desirable to maintain normal serum potassium and magnesium concentrations in patients being
195 treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or
196 prolonged vomiting, as well as the use of the following drugs or procedures: diuretics,
197 amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal
198 secretions.

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

205 **Use in Thyroid Disorders and Hypermetabolic States:** Hypothyroidism may reduce the
206 requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic
207 or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated
208 by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states
209 are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is
210 used.

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

214 **Use During Electrical Cardioversion:** It may be desirable to reduce the dose of digoxin for
215 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of
216 ventricular arrhythmias, but physicians must consider the consequences of increasing the
217 ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective
218 cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible
219 energy level should be selected to avoid provoking ventricular arrhythmias.

220 **Use in Patients With Myocarditis:** Digoxin can rarely precipitate vasoconstriction and
221 therefore should be avoided in patients with myocarditis.

222 **Use in Patients With Beri Beri Heart Disease:** Patients with beri beri heart disease may
223 fail to respond adequately to digoxin if the underlying thiamine deficiency is not treated
224 concomitantly.

225 **Laboratory Test Monitoring:** Patients receiving digoxin should have their serum electrolytes
226 and renal function (serum creatinine concentrations) assessed periodically; the frequency of
227 assessments will depend on the clinical setting. For discussion of serum digoxin concentrations,
228 see DOSAGE AND ADMINISTRATION.

229 **Drug Interactions:** Potassium-depleting *diuretics* are a major contributing factor to digitalis
230 toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce
231 serious arrhythmias in digitalized patients. *Quinidine*, *verapamil*, *amiodarone*, *propafenone*,
232 *indomethacin*, *itraconazole*, *alprazolam*, and *spironolactone* raise the serum digoxin

233 concentration due to a reduction in clearance and/or volume of distribution of the drug, with the
234 implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly
235 other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who
236 inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication
237 may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin
238 absorption. *Antacids*, *kaolin-pectin*, *sulfasalazine*, *neomycin*, *cholestyramine*, certain *anticancer*
239 *drugs*, and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in
240 unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration,
241 especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin.
242 There have been inconsistent reports regarding the effects of other drugs (e.g., *quinine*,
243 *Penicillamine*) on serum digoxin concentration. *Thyroid* administration to a digitalized,
244 hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin
245 and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may cause a
246 sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in
247 digitalized patients. Although calcium channel blockers and digoxin may be useful in
248 combination to control atrial fibrillation, their additive effects on AV node conduction can result
249 in advanced or complete heart block. Both digitalis glycosides and beta-blockers slow
250 atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of
251 bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol
252 are administered concomitantly. Therefore, increased monitoring of digoxin is recommended
253 when initiating, adjusting, or discontinuing carvedilol.

254 Due to the considerable variability of these interactions, dosage of digoxin should be
255 individualized when patients receive these medications concurrently. Furthermore, caution
256 should be exercised when combining digoxin with any drug that may cause a significant
257 deterioration in renal function, since a decline in glomerular filtration or tubular secretion may
258 impair the excretion of digoxin.

259 **Drug/Laboratory Test Interactions:** The use of therapeutic doses of digoxin may cause
260 prolongation of the PR interval and depression of the ST segment on the electrocardiogram.
261 Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise
262 testing. These electrophysiologic effects reflect an expected effect of the drug and are not
263 indicative of toxicity.

264 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Digoxin showed no genotoxic
265 potential in *in vitro* studies (Ames test and mouse lymphoma). No data are available on the
266 carcinogenic potential of digoxin, nor have studies been conducted to assess its potential to affect
267 fertility.

268 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Animal reproduction studies have
269 not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm
270 when administered to a pregnant woman or can affect reproductive capacity. Digoxin should be
271 given to a pregnant woman only if clearly needed.

272 **Nursing Mothers:** Studies have shown that digoxin concentrations in the mother's serum and
273 milk are similar. However, the estimated exposure of a nursing infant to digoxin via
274 breastfeeding will be far below the usual infant maintenance dose. Therefore, this amount should
275 have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when
276 digoxin is administered to a nursing woman.

277 **Pediatric Use:** Newborn infants display considerable variability in their tolerance to digoxin.
278 Premature and immature infants are particularly sensitive to the effects of digoxin, and the
279 dosage of the drug must not only be reduced but must be individualized according to their degree
280 of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

281 **Geriatric Use:** The majority of clinical experience gained with digoxin has been in the elderly
282 population. This experience has not identified differences in response or adverse effects between
283 the elderly and younger patients. However, this drug is known to be substantially excreted by the
284 kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal
285 function. Because elderly patients are more likely to have decreased renal function, care should
286 be taken in dose selection, which should be based on renal function, and it may be useful to
287 monitor renal function.

288 **ADVERSE REACTIONS**

289 In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than
290 those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when
291 digoxin is used within the recommended dose range or therapeutic serum concentration range
292 and when there is careful attention to concurrent medications and conditions.

293 Because some patients may be particularly susceptible to side effects with digoxin, the dosage
294 of the drug should always be selected carefully and adjusted as the clinical condition of the
295 patient warrants. In the past, when high doses of digoxin were used and little attention was paid
296 to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and
297 severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for
298 about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.
299 However, available evidence suggests that the incidence and severity of digoxin toxicity has
300 decreased substantially in recent years. In recent controlled clinical trials, in patients with
301 predominantly mild to moderate heart failure, the incidence of adverse experiences was
302 comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the
303 incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking LANOXIN
304 Tablets compared to 0.9% in patients taking placebo. In this trial, the most common
305 manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS
306 manifestations were less common.

307 **Adults: Cardiac:** Therapeutic doses of digoxin may cause heart block in patients with pre-
308 existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose
309 of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block
310 is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances,

311 such as first-degree, second-degree (Wenckebach), or third-degree heart block (including
 312 asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm;
 313 unifocal or multifocal premature contractions (especially bigeminy or trigeminy);
 314 ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST
 315 segment depression which should not by themselves be considered digoxin toxicity. Cardiac
 316 toxicity can also occur at therapeutic doses in patients who have conditions which may alter their
 317 sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

318 **Gastrointestinal:** Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the
 319 use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic
 320 necrosis of the intestines.

321 **CNS:** Digoxin can produce visual disturbances (blurred or yellow vision), headache,
 322 weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression,
 323 delirium, and hallucination).

324 **Other:** Gynecomastia has been occasionally observed following the prolonged use of
 325 digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely
 326 observed.

327 Table 4 summarizes the incidence of those adverse experiences listed above for patients
 328 treated with LANOXIN Tablets or placebo from 2 randomized, double-blind, placebo-controlled
 329 withdrawal trials. Patients in these trials were also receiving diuretics with or without
 330 angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were
 331 randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients
 332 following dosage titration with the use of serum digoxin concentrations and careful follow-up.
 333 These adverse experiences are consistent with results from a large, placebo-controlled mortality
 334 trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.
 335

336 **Table 4. Adverse Experiences In 2 Parallel, Double-Blind, Placebo-Controlled Withdrawal**
 337 **Trials (Number of Patients Reporting)**

Adverse Experience	Digoxin Patients (n = 123)	Placebo Patients (n = 125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6

CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

338

339 **Infants and Children:** The side effects of digoxin in infants and children differ from those
340 seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting,
341 diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of
342 overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with
343 digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus
344 bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are
345 conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or
346 without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common.
347 Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in
348 the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that
349 develops in a child taking digoxin should be assumed to be caused by digoxin, until further
350 evaluation proves otherwise.

351 **OVERDOSAGE**

352 **Signs and Symptoms:** The signs and symptoms of toxicity are generally similar to those
353 described in the ADVERSE REACTIONS section but may be more frequent and can be more
354 severe. Signs and symptoms of digoxin toxicity become more frequent with levels above
355 2 ng/mL. However, in deciding whether a patient's symptoms are due to digoxin, the clinical
356 state together with serum electrolyte levels and thyroid function are important factors (see
357 DOSAGE AND ADMINISTRATION).

358 **Adults:** In adults without heart disease, clinical observation suggests that an overdose of
359 digoxin of 10 to 15 mg was the dose resulting in death of half of the patients. If more than 25 mg
360 of digoxin was ingested by an adult without heart disease, death or progressive toxicity
361 responsive only to digoxin-binding Fab antibody fragments resulted. Cardiac manifestations are
362 the most frequent and serious sign of both acute and chronic toxicity. Peak cardiac effects
363 generally occur 3 to 6 hours following overdosage and may persist for the ensuing 24 hours or
364 longer. Digoxin toxicity may result in almost any type of arrhythmia (see ADVERSE
365 REACTIONS). Multiple rhythm disturbances in the same patient are common. Cardiac arrest
366 from asystole or ventricular fibrillation due to digoxin toxicity is usually fatal.

367 Among the extra-cardiac manifestations, gastrointestinal symptoms (e.g. nausea, vomiting,
368 anorexia) are very common (up to 80% incidence) and precede cardiac manifestations in
369 approximately half of the patients in most literature reports. Neurologic manifestations (e.g.

370 dizziness, various CNS disturbances), fatigue, and malaise are very common. Visual
371 manifestations may also occur with aberration in color vision (predominance of yellow green)
372 the most frequent. Neurological and visual symptoms may persist after other signs of toxicity
373 have resolved. In chronic toxicity, non-specific extra-cardiac symptoms, such as malaise and
374 weakness, may predominate.

375 **Children:** In children aged 1 to 3 years without heart disease, clinical observation suggests
376 that an overdose of digoxin of 6 to 10 mg was the dose resulting in death in half of the patients.
377 If more than 10 mg of digoxin was ingested by a child aged 1 to 3 years without heart disease,
378 the outcome was uniformly fatal when Fab fragment treatment was not given. Most
379 manifestations of toxicity in children occur during or shortly after the loading phase with
380 digoxin. The same arrhythmias or combination of arrhythmias that occur in adults can occur in
381 pediatrics. Sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen
382 less frequently in the pediatric population. Pediatric patients are more likely to present with an
383 AV conduction disturbance or a sinus bradycardia. Any arrhythmia or alteration in cardiac
384 conduction that develops in a child taking digoxin should be assumed to be caused by digoxin,
385 until further evaluation proves otherwise.

386 The frequent extracardiac manifestations similar to those seen in adults are gastrointestinal,
387 CNS, and visual. However, nausea and vomiting are not frequent in infants and small children.

388 In addition to the undesirable effects seen with recommended doses, weight loss in older age
389 groups and failure to thrive in infants, abdominal pain due to mesenteric artery ischemia,
390 drowsiness, and behavioral disturbances including psychotic manifestations have been reported
391 in overdose.

392 **Treatment:** In addition to cardiac monitoring, digoxin should be temporarily discontinued until
393 the adverse reaction resolves and may be all that is required to treat the adverse reaction such as
394 in asymptomatic bradycardia or digoxin related heart block. Every effort should also be made to
395 correct factors that may contribute to the adverse reaction (such as electrolyte disturbances,
396 thyroid function, or concurrent medications) (see WARNINGS and PRECAUTIONS: Drug
397 Interactions). Once the adverse reaction has resolved, therapy with digoxin may be reinstated,
398 following a careful reassessment of dose.

399 When the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional
400 therapy may be needed.

401 If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration
402 should be given to the reversal of toxicity with Digoxin Immune Fab (Ovine) [DIGIBIND[®] or
403 DIGIFAB[®]] (see Massive Digitalis Overdosage subsection), the use of atropine, or the insertion
404 of a temporary cardiac pacemaker. Digoxin Immune Fab (Ovine) is a specific antidote for
405 digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to
406 digoxin overdosage.

407 If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the
408 correction of electrolyte disorders, particularly if hypokalemia (see Administration of Potassium

409 subsection) or hypomagnesemia is present. Ventricular arrhythmias may respond to lidocaine or
410 phenytoin.

411 **Administration of Potassium:** Before administering potassium in digoxin overdose for
412 hypokalemia, the serum potassium must be known and every effort should be made to maintain
413 the serum potassium concentration between 4 and 5.5 mmol/L. Potassium salts should be
414 avoided as they may be dangerous in patients who manifest bradycardia or heart block due to
415 digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive
416 digitalis overdosage. Potassium is usually administered orally, but when correction of the
417 arrhythmia is urgent and the serum potassium concentration is low, potassium may be
418 administered cautiously by the intravenous route. The electrocardiogram should be monitored for
419 any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the
420 arrhythmia.

421 **Massive Digitalis Overdosage:** Manifestations of life-threatening toxicity include
422 ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart
423 block.

424 Digoxin Immune Fab (Ovine) should be used to reverse the toxic effects of ingestion of a
425 massive overdose. The decision to administer Digoxin Immune Fab (Ovine) to a patient who has
426 ingested a massive dose of digoxin but who has not yet manifested life-threatening toxicity
427 should depend on the likelihood that life-threatening toxicity will occur (see above).

428 Digoxin is not effectively removed from the body by dialysis due to its large extravascular
429 volume of distribution. Patients with massive digitalis ingestion should receive large doses of
430 activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric
431 recirculation. Emesis may be indicated especially if ingestion has occurred within 30 minutes of
432 the patient's presentation at the hospital. Emesis should not be induced in patients who are
433 obtunded. If a patient presents more than 2 hours after ingestion or already has toxic
434 manifestations, it may be unsafe to induce vomiting because such maneuvers may induce an
435 acute vagal episode that can worsen digitalis-related arrhythmias.

436 In cases where a large amount of digoxin has been ingested, hyperkalemia may be present due
437 to release of potassium from skeletal muscle. Hyperkalemia caused by massive digitalis toxicity
438 is best treated with Digoxin Immune Fab (Ovine); initial treatment with glucose and insulin may
439 also be required if hyperkalemia itself is acutely life-threatening.

440 **DOSAGE AND ADMINISTRATION**

441 **General:** Recommended dosages of digoxin may require considerable modification because of
442 individual sensitivity of the patient to the drug, the presence of associated conditions, or the use
443 of concurrent medications.

444 Parenteral administration of digoxin should be used only when the need for rapid
445 digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead
446 to severe pain at the injection site, thus intravenous administration is preferred. If the drug must

447 be administered by the intramuscular route, it should be injected deep into the muscle followed
448 by massage. No more than 200 mcg (2 mL) should be injected into a single site.

449 LANOXIN Injection Pediatric can be administered undiluted or diluted with a 4-fold or
450 greater volume of Sterile Water for Injection, 0.9% Sodium Chloride Injection, or 5% Dextrose
451 Injection. The use of less than a 4-fold volume of diluent could lead to precipitation of the
452 digoxin. Immediate use of the diluted product is recommended.

453 If tuberculin syringes are used to measure very small doses, one must be aware of the problem
454 of inadvertent overadministration of digoxin. The syringe should *not* be flushed with the
455 parenteral solution after its contents are expelled into an indwelling vascular catheter.

456 Slow infusion of LANOXIN Injection Pediatric is preferable to bolus administration. Rapid
457 infusion of digitalis glycosides has been shown to cause systemic and coronary arteriolar
458 constriction, which may be clinically undesirable. Caution is thus advised and LANOXIN
459 Injection Pediatric should probably be administered over a period of 5 minutes or longer. Mixing
460 of LANOXIN Injection Pediatric with other drugs in the same container or simultaneous
461 administration in the same intravenous line is not recommended.

462 In selecting a dose of digoxin, the following factors must be considered:

- 463 1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body
464 weight.
- 465 2. The patient's renal function, preferably evaluated on the basis of estimated creatinine
466 clearance.
- 467 3. The patient's age. Infants and children require different doses of digoxin than adults. Also,
468 advanced age may be indicative of diminished renal function even in patients with normal
469 serum creatinine concentration (i.e., below 1.5 mg/dL).
- 470 4. Concomitant disease states, concurrent medications, or other factors likely to alter the
471 pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

472 **Serum Digoxin Concentrations:** In general, the dose of digoxin used should be determined
473 on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to
474 the clinician in determining the adequacy of digoxin therapy and in assigning certain
475 probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered
476 adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging
477 from 0.8 to 2.0 ng/mL. However, digoxin may produce clinical benefits even at serum
478 concentrations below this range. About two-thirds of adult patients with clinical toxicity have
479 serum digoxin concentrations greater than 2.0 ng/mL. However, since one-third of patients with
480 clinical toxicity have concentrations less than 2.0 ng/mL, values below 2.0 ng/mL do not rule out
481 the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are
482 patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL.
483 Consequently, the serum concentration of digoxin should always be interpreted in the overall
484 clinical context, and an isolated measurement should not be used alone as the basis for increasing
485 or decreasing the dose of the drug.

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

494 If a discrepancy exists between the reported serum concentration and the observed clinical
495 response, the clinician should consider the following possibilities:

- 496 1. Analytical problems in the assay procedure.
- 497 2. Inappropriate serum sampling time.
- 498 3. Administration of a digitalis glycoside other than digoxin.
- 499 4. Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the
500 sensitivity of the patient to digoxin.
- 501 5. Serum digoxin concentration may decrease acutely during periods of exercise without any
502 associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

503 **Heart Failure: Adults:** See the full prescribing information for LANOXIN Injection for
504 specific recommendations.

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

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

- 516 1. If rapid digitalization is considered medically appropriate, it may be achieved by
517 administering a loading dose based upon projected peak digoxin body stores. Maintenance
518 dose can be calculated as a percentage of the loading dose.
- 519 2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose,
520 thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin
521 concentrations will be achieved in approximately five half-lives of the drug for the individual
522 patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

523 **Rapid Digitalization With a Loading Dose:** LANOXIN Injection Pediatric can be
524 used to achieve rapid digitalization, with conversion to an oral formulation of LANOXIN for
525 maintenance therapy. If patients are switched from intravenous to oral digoxin formulations,

526 allowances must be made for differences in bioavailability when calculating maintenance
527 dosages (see Table 1 in CLINICAL PHARMACOLOGY: Pharmacokinetics and dosing Table
528 5).

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

531 Peak digoxin body stores of 8 to 12 mcg/kg should provide therapeutic effect with minimum
532 risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered
533 digoxin distribution and elimination, projected peak body stores for patients with renal
534 insufficiency should be conservative (i.e., 6 to 10 mcg/kg) (see PRECAUTIONS).

535 Digitalizing and daily maintenance doses for each age group are given in Table 5 and should
536 provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and
537 normal sinus rhythm. These recommendations assume the presence of normal renal function.

538 The loading dose should be administered in several portions, with roughly half the total given
539 as the first dose. Additional fractions of this planned total dose may be given at 4- to 8-hour
540 intervals, **with careful assessment of clinical response before each additional dose.** If the
541 patient's clinical response necessitates a change from the calculated loading dose of digoxin,
542 then calculation of the maintenance dose should be based upon the amount actually given.

543

544 **Table 5. Usual Digitalizing and Maintenance Dosages for LANOXIN® Injection Pediatric in**
545 **Children With Normal Renal Function Based on Lean Body Weight**

Age	IV Digitalizing ^a Dose (mcg/kg)	Daily IV Maintenance Dose ^b (mcg/kg)
Premature	15 to 25	20% to 30% of the IV digitalizing dose ^c
Full-Term	20 to 30	25% to 35% of the IV digitalizing dose ^c
1 to 24 Months	30 to 50	
2 to 5 Years	25 to 35	
5 to 10 Years	15 to 30	
Over 10 Years	8 to 12	

546 ^a IV digitalizing doses are 80% of oral digitalizing doses.

547 ^b Divided daily dosing is recommended for children under 10 years of age.

548 ^c Projected or actual digitalizing dose providing clinical response.

549

550 In children with renal disease, digoxin dosing must be carefully titrated based on clinical
551 response.

552 **Gradual Digitalization With A Maintenance Dose:** More gradual digitalization can
553 also be accomplished by beginning an appropriate maintenance dose. The range of percentages
554 provided in Table 5 can be used in calculating this dose for patients with normal renal function.

555 **It cannot be overemphasized that these pediatric dosage guidelines are based upon**
556 **average patient response and substantial individual variation can be expected.**

557 **Accordingly, ultimate dosage selection must be based upon clinical assessment of the**
558 **patient.**

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

565 **Dosage Adjustment When Changing Preparations:** The differences in bioavailability
566 between injectable LANOXIN or LANOXIN Tablets must be considered when changing
567 patients from one dosage form to another.

568 **HOW SUPPLIED**

569 LANOXIN (digoxin) Injection Pediatric, 100 mcg (0.1 mg) in 1 mL; box of 10 ampuls (NDC
570 0173-0262-10).

571 **Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP**
572 **Controlled Room Temperature] and protect from light.**

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575 DIGIFAB is a registered trademark of Prostherics Inc.
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578 Manufactured by
579 DSM Pharmaceuticals, Inc.
580 Greenville, NC 27834 for
581 GlaxoSmithKline
582 Research Triangle Park, NC 27709
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