

1 PRESCRIBING INFORMATION

2 **LANOXIN<sup>®</sup>**

3 **(digoxin) Tablets, USP**

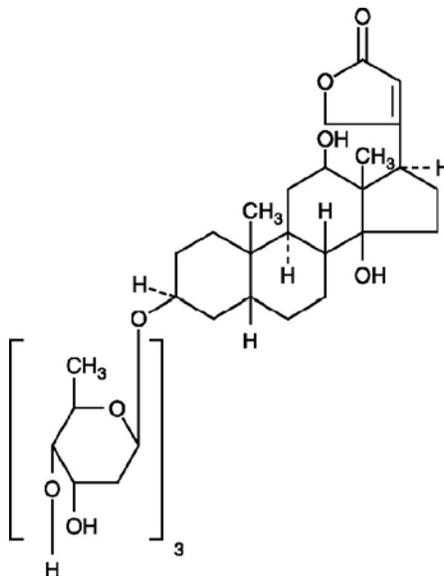
4 **125 mcg (0.125 mg) Scored I.D. Imprint Y3B (yellow)**

5 **250 mcg (0.25 mg) Scored I.D. Imprint X3A (white)**

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 C<sub>41</sub>H<sub>64</sub>O<sub>14</sub>,  
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 is supplied as 125-mcg (0.125-mg) or 250-mcg (0.25-mg) tablets for oral  
23 administration. Each tablet contains the labeled amount of digoxin USP and the following  
24 inactive ingredients: corn and potato starches, lactose, and magnesium stearate. In addition, the  
25 dyes used in the 125-mcg (0.125-mg) tablets are D&C Yellow No. 10 and FD&C Yellow No. 6.

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: Absorption:** Following oral administration, peak serum concentrations  
47 of digoxin occur at 1 to 3 hours. Absorption of digoxin from LANOXIN Tablets has been  
48 demonstrated to be 60% to 80% complete compared to an identical intravenous dose of digoxin  
49 (absolute bioavailability). When LANOXIN Tablets are taken after meals, the rate of absorption  
50 is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with  
51 meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced.  
52 Comparisons of the systemic availability and equivalent doses for oral preparations of  
53 LANOXIN are shown in Table 1.

54

55 **Table 1. Comparisons of the Systemic Availability and Equivalent Doses for Oral**  
56 **Preparations of LANOXIN**

Product	Absolute Bioavailability	Equivalent Doses (mcg) <sup>a</sup> 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

57 <sup>a</sup> For example, 125-mcg LANOXIN Tablets equivalent to 100-mcg LANOXIN Injection/IV.

58

59 In some patients, orally administered digoxin is converted to inactive reduction products (e.g.,  
60 dihydrodigoxin) by colonic bacteria in the gut. Data suggest that 1 in 10 patients treated with  
61 digoxin tablets will degrade 40% or more of the ingested dose. As a result, certain antibiotics

62 may increase the absorption of digoxin in such patients. Although inactivation of these bacteria  
63 by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the  
64 elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to  
65 the extent of bacterial inactivation, and may be as much as 2-fold in some cases.

66 **Distribution:** Following drug administration, a 6- to 8-hour tissue distribution phase is  
67 observed. This is followed by a much more gradual decline in the serum concentration of the  
68 drug, which is dependent on the elimination of digoxin from the body. The peak height and slope  
69 of the early portion (absorption/distribution phases) of the serum concentration-time curve are  
70 dependent upon the route of administration and the absorption characteristics of the formulation.  
71 Clinical evidence indicates that the early high serum concentrations do not reflect the  
72 concentration of digoxin at its site of action, but that with chronic use, the steady-state  
73 post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate  
74 with pharmacologic effects. In individual patients, these post-distribution serum concentrations  
75 may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND  
76 ADMINISTRATION: Serum Digoxin Concentrations).

77 Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution.  
78 Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin  
79 concentration in the newborn is similar to the serum concentration in the mother. Approximately  
80 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not  
81 significantly altered by large changes in fat tissue weight, so that its distribution space correlates  
82 best with lean (i.e., ideal) body weight, not total body weight.

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

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

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

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

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

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

110

111 **Table 2. Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of**  
112 **LANOXIN**

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

113 <sup>a</sup> Documented for ventricular response rate in atrial fibrillation, inotropic effects and  
114 electrocardiographic changes.

115 <sup>b</sup> Depending upon rate of infusion.

116

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

122 **Chronic Heart Failure:** Two 12-week, double-blind, placebo-controlled studies enrolled  
123 178 (RADIANCE trial) and 88 (PROVED trial) patients with NYHA class II or III heart failure  
124 previously treated with digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and  
125 randomized them to placebo or treatment with LANOXIN. Both trials demonstrated better  
126 preservation of exercise capacity in patients randomized to LANOXIN. Continued treatment  
127 with LANOXIN reduced the risk of developing worsening heart failure, as evidenced by heart  
128 failure-related hospitalizations and emergency care and the need for concomitant heart failure  
129 therapy. The larger study also showed treatment-related benefits in NYHA class and patients'  
130 global assessment. In the smaller trial, these trended in favor of a treatment benefit.

131 The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized,  
132 double-blind, placebo-controlled mortality study of 6,801 patients with heart failure and left  
133 ventricular ejection fraction  $\leq 0.45$ . At randomization, 67% were NYHA class I or II, 71% had  
134 heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving  
135 concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or  
136 LANOXIN, the dose of which was adjusted for the patient's age, sex, lean body weight, and  
137 serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months

138 (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality  
 139 was 35% with no difference between groups (95% confidence limits for relative risk of 0.91 to  
 140 1.07). LANOXIN was associated with a 25% reduction in the number of hospitalizations for  
 141 heart failure, a 28% reduction in the risk of a patient having at least 1 hospitalization for heart  
 142 failure, and a 6.5% reduction in total hospitalizations (for any cause).

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

148

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

	n	Risk of All-Cause Mortality or All-Cause Hospitalization <sup>a</sup>			Risk of HF-Related Mortality or HF-Related Hospitalization <sup>a</sup>		
		Placebo	LANOXIN	Relative risk <sup>b</sup>	Placebo	LANOXIN	Relative risk <sup>b</sup>
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 <sup>c</sup>	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

151 <sup>a</sup> Number of patients with an event during the first 2 years per 1,000 randomized patients.

152 <sup>b</sup> Relative risk (95% confidence interval).

153 <sup>c</sup> DIG Ancillary Study.

154

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

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

## 161 **INDICATIONS AND USAGE**

162 **Heart Failure:** LANOXIN is indicated for the treatment of mild to moderate heart failure.  
163 LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as  
164 evidenced by exercise capacity and heart failure-related hospitalizations and emergency care,  
165 while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic  
166 and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these 3 drugs  
167 cannot be specified.

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

## 170 **CONTRAINDICATIONS**

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

## 174 **WARNINGS**

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

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

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

195 **PRECAUTIONS**

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

204 **Use in Patients With Electrolyte Disorders:** In patients with hypokalemia or  
205 hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL,  
206 because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is  
207 desirable to maintain normal serum potassium and magnesium concentrations in patients being  
208 treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or  
209 prolonged vomiting, as well as the use of the following drugs or procedures: diuretics,  
210 amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal  
211 secretions.

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

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

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

227 **Use During Electrical Cardioversion:** It may be desirable to reduce the dose of digoxin for  
228 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of  
229 ventricular arrhythmias, but physicians must consider the consequences of increasing the  
230 ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective  
231 cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible  
232 energy level should be selected to avoid provoking ventricular arrhythmias.

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

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

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

242 **Drug Interactions:** Potassium-depleting *diuretics* are a major contributing factor to digitalis  
243 toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce  
244 serious arrhythmias in digitalized patients. *Quinidine*, *verapamil*, *amiodarone*, *propafenone*,  
245 *indomethacin*, *itraconazole*, *alprazolam*, and *spironolactone* raise the serum digoxin  
246 concentration due to a reduction in clearance and/or in volume of distribution of the drug, with  
247 the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and  
248 possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in  
249 patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis  
250 intoxication may result (see CLINICAL PHARMACOLOGY: Absorption). *Propantheline* and  
251 *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids*, *kaolin-*  
252 *pectin*, *sulfasalazine*, *neomycin*, *cholestyramine*, certain *anticancer drugs*, and *metoclopramide*  
253 may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum  
254 concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with  
255 renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent  
256 reports regarding the effects of other drugs [e.g., *quinine*, *penicillamine*] on serum digoxin  
257 concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose  
258 requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of  
259 cardiac arrhythmias. *Succinylcholine* may cause a sudden extrusion of potassium from muscle  
260 cells, and may thereby cause arrhythmias in digitalized patients. Although calcium channel  
261 blockers and digoxin may be useful in combination to control atrial fibrillation, their additive  
262 effects on AV node conduction can result in advanced or complete heart block. Both digitalis  
263 glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate.  
264 Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by  
265 about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased  
266 monitoring of digoxin is recommended when initiating, adjusting, or discontinuing carvedilol.

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

272 **Drug/Laboratory Test Interactions:** The use of therapeutic doses of digoxin may cause  
273 prolongation of the PR interval and depression of the ST segment on the electrocardiogram.  
274 Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise

275 testing. These electrophysiologic effects reflect an expected effect of the drug and are not  
276 indicative of toxicity.

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

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

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

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

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

## 301 **ADVERSE REACTIONS**

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

306 Because some patients may be particularly susceptible to side effects with digoxin, the dosage  
307 of the drug should always be selected carefully and adjusted as the clinical condition of the  
308 patient warrants. In the past, when high doses of digoxin were used and little attention was paid  
309 to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and  
310 severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for  
311 about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.  
312 However, available evidence suggests that the incidence and severity of digoxin toxicity has  
313 decreased substantially in recent years. In recent controlled clinical trials, in patients with

314 predominantly mild to moderate heart failure, the incidence of adverse experiences was  
315 comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the  
316 incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking LANOXIN  
317 compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of  
318 digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less  
319 common.

320 **Adults: Cardiac:** Therapeutic doses of digoxin may cause heart block in patients with  
321 pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the  
322 dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart  
323 block is considered unacceptable. High doses of digoxin may produce a variety of rhythm  
324 disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block  
325 (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional  
326 (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or  
327 trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR  
328 prolongation and ST segment depression which should not by themselves be considered digoxin  
329 toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions  
330 which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

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

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

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

340 Table 4 summarizes the incidence of those adverse experiences listed above for patients  
341 treated with LANOXIN Tablets or placebo from 2 randomized, double-blind, placebo-controlled  
342 withdrawal trials. Patients in these trials were also receiving diuretics with or without  
343 angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were  
344 randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients  
345 following dosage titration with the use of serum digoxin concentrations and careful follow-up.  
346 These adverse experiences are consistent with results from a large, placebo-controlled mortality  
347 trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.  
348

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

Adverse Experience	Digoxin Patients (n = 123)	Placebo Patients (n = 125)
<b>Cardiac</b>		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
<b>Gastrointestinal</b>		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
<b>CNS</b>		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
<b>Other</b>		
Rash	2	1
Death	4	3

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

364 **OVERDOSAGE**

365 **Signs and Symptoms:** The signs and symptoms of toxicity are generally similar to those  
 366 described in the ADVERSE REACTIONS section but may be more frequent and can be more  
 367 severe. Signs and symptoms of digoxin toxicity become more frequent with levels above

368 2 ng/mL. However, in deciding whether a patient's symptoms are due to digoxin, the clinical  
369 state together with serum electrolyte levels and thyroid function are important factors (see  
370 DOSAGE AND ADMINISTRATION).

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

380 Among the extra-cardiac manifestations, gastrointestinal symptoms (e.g. nausea, vomiting,  
381 anorexia) are very common (up to 80% incidence) and precede cardiac manifestations in  
382 approximately half of the patients in most literature reports. Neurologic manifestations (e.g.  
383 dizziness, various CNS disturbances), fatigue, and malaise are very common. Visual  
384 manifestations may also occur with aberration in color vision (predominance of yellow green)  
385 the most frequent. Neurological and visual symptoms may persist after other signs of toxicity  
386 have resolved. In chronic toxicity, non-specific extra-cardiac symptoms, such as malaise and  
387 weakness, may predominate.

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

399 The frequent extracardiac manifestations similar to those seen in adults are gastrointestinal,  
400 CNS, and visual. However, nausea and vomiting are not frequent in infants and small children.  
401 In addition to the undesirable effects seen with recommended doses, weight loss in older age  
402 groups and failure to thrive in infants, abdominal pain due to mesenteric artery ischemia,  
403 drowsiness, and behavioral disturbances including psychotic manifestations have been reported  
404 in overdose.

405 **Treatment:** In addition to cardiac monitoring, digoxin should be temporarily discontinued until  
406 the adverse reaction resolves and may be all that is required to treat the adverse reaction such as  
407 in asymptomatic bradycardia or digoxin-related heart block. Every effort should also be made to

408 correct factors that may contribute to the adverse reaction (such as electrolyte disturbances,  
409 thyroid function, or concurrent medications) (see WARNINGS and PRECAUTIONS: Drug  
410 Interactions). Once the adverse reaction has resolved, therapy with digoxin may be reinstated,  
411 following a careful reassessment of dose.

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

414 If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration  
415 should be given to the reversal of toxicity with Digoxin Immune Fab (Ovine) [DIGIBIND<sup>®</sup> or  
416 DIGIFAB<sup>®</sup>] (see Massive Digitalis Overdosage subsection), the use of atropine, or the insertion  
417 of a temporary cardiac pacemaker. Digoxin Immune Fab (Ovine) is a specific antidote for  
418 digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to  
419 digoxin overdosage.

420 If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the  
421 correction of electrolyte disorders, particularly if hypokalemia (see Administration of Potassium  
422 subsection) or hypomagnesemia is present. Ventricular arrhythmias may respond to lidocaine or  
423 phenytoin.

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

434 **Massive Digitalis Overdosage:** Manifestations of life-threatening toxicity include  
435 ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart  
436 block.

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

441 Digoxin is not effectively removed from the body by dialysis due to its large extravascular  
442 volume of distribution. Patients with massive digitalis ingestion should receive large doses of  
443 activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric  
444 recirculation. Emesis may be indicated especially if ingestion has occurred within 30 minutes of  
445 the patient's presentation at the hospital. Emesis should not be induced in patients who are  
446 obtunded. If a patient presents more than 2 hours after ingestion or already has toxic

447 manifestations, it may be unsafe to induce vomiting because such maneuvers may induce an  
448 acute vagal episode that can worsen digitalis-related arrhythmias.

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

## 453 **DOSAGE AND ADMINISTRATION**

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

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

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

482 To allow adequate time for equilibration of digoxin between serum and tissue, sampling of  
483 serum concentrations should be done just before the next scheduled dose of the drug. If this is  
484 not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the  
485 route of administration or the formulation used. On a once-daily dosing schedule, the

486 concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours,  
487 depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only  
488 minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours  
489 after a dose.

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

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

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

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

509 **Rapid Digitalization With a Loading Dose:** Peak digoxin body stores of 8 to  
510 12 mcg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with  
511 heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination,  
512 projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to  
513 10 mcg/kg) (see PRECAUTIONS).

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

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

520 A single initial dose of 500 to 750 mcg (0.5 to 0.75 mg) of LANOXIN Tablets usually  
521 produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours.  
522 Additional doses of 125 to 375 mcg (0.125 to 0.375 mg) may be given cautiously at 6- to  
523 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount  
524 of LANOXIN Tablets that a 70-kg patient requires to achieve 8 to 12 mcg/kg peak body  
525 stores is 750 to 1,250 mcg (0.75 to 1.25 mg).

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

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

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

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

$$546 \text{ Maintenance Dose} = \text{Peak Body Stores (i.e., Loading Dose)} \times \% \text{ Daily Loss}/100$$

$$547 \text{ Where: } \% \text{ Daily Loss} = 14 + \text{Ccr}/5$$

548 (Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m<sup>2</sup> body surface area.)

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

551

552 **Table 5. Usual Daily Maintenance Dose Requirements (mcg) of LANOXIN for Estimated**  
 553 **Peak Body Stores of 10 mcg/kg**

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

554 <sup>a</sup> Ccr is creatinine clearance, corrected to 70-kg body weight or 1.73 m<sup>2</sup> body surface area.

555 *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to  
 556 70 kg body weight) may be estimated in men as (140 - Age)/Scr. For women, this result  
 557 should be multiplied by 0.85. *Note:* This equation cannot be used for estimating creatinine  
 558 clearance in infants or children.

559 <sup>b</sup> If no loading dose administered.

560 <sup>c</sup> 62.5 mcg = 0.0625 mg.

561

562 **Example:** Based on Table 5, a patient in heart failure with an estimated lean body weight of  
 563 70 kg and a Ccr of 60 mL/min should be given a dose of 250 mcg (0.25 mg) daily of LANOXIN  
 564 Tablets, usually taken after the morning meal. If no loading dose is administered, steady-state  
 565 serum concentrations in this patient should be anticipated at approximately 11 days.

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

573 Daily maintenance doses for each age group are given in Table 6 and should provide  
 574 therapeutic effects with minimum risk of toxicity in most patients with heart failure and normal  
 575 sinus rhythm. These recommendations assume the presence of normal renal function:

576

577 **Table 6. Daily Maintenance Doses in Children With Normal Renal Function**

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

578  
579 In children with renal disease, digoxin must be carefully titrated based upon clinical response.

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

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

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

### 593 **HOW SUPPLIED**

594 LANOXIN (digoxin) Tablets, Scored 125 mcg (0.125 mg): Bottles of 100 with child-resistant  
595 cap (NDC 0173-0242-55) and 1,000 (NDC 0173-0242-75); unit dose pack of 100 (NDC 0173-  
596 0242-56). Imprinted with LANOXIN and Y3B (yellow).

597 **Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP**  
598 **Controlled Room Temperature] in a dry place and protect from light.**

599  
600 LANOXIN (digoxin) Tablets, Scored 250 mcg (0.25 mg): Bottles of 100 with child-resistant cap  
601 (NDC 0173-0249-55), 1,000 (NDC 0173-0249-75), and 5,000 (NDC 0173-0249-80); unit dose  
602 pack of 100 (NDC 0173-0249-56). Imprinted with LANOXIN and X3A (white).

603 **Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP**  
604 **Controlled Room Temperature] in a dry place.**

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