CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021648Orig1s004

Trade Name: Digoxin Oral Solution USP, 0.05 mg/mL

Generic Name: Digoxin

Sponsor: Roxane Laboratories, Inc.

Approval Date: September 26, 2011

Indications: Provides for the conversion of the digoxin label to the Physician Labeling Rule (PLR) format. Editorial changes were made throughout the label; significant specific content changes were made to sections 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14 and 17

CENTER FOR DRUG EVALUATION AND RESEARCH

021648Orig1s004

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21648/S-004

SUPPLEMENT APPROVAL

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products
1809 Wilson Rd.
Columbus, OH 43228

Dear Ms. Ernst:

Please refer to your Supplemental New Drug Application (sNDA) dated June 11, 2010, received June 14, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Digoxin Oral Solution USP, 0.05 mg/mL.

We acknowledge receipt of your amendments dated June 18, and October 5, 2010 and September 22, 2011.

This "Prior Approval" supplemental new drug application provides for the conversion of the digoxin label to the Physician Labeling Rule (PLR) format. Editorial changes were made throughout the label; significant specific content changes were made to sections 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14 and 17.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below:

1. Remove the word (b) (4) from the title and table in Table 1.
2. The dosing regimen was clarified in the right column in Table 2.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Alexis Childers, Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
09/26/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Digoxin Oral Solution, USP safely and effectively. See full prescribing information for Digoxin Oral Solution, USP.

Digoxin Oral Solution, USP
Initial U.S. Approval: 1982

----------INDICATIONS AND USAGE----------

In adults, digoxin is indicated for the treatment of mild to moderate heart failure and for the control of resting ventricular rate in patients with chronic atrial fibrillation. (1). In pediatric patients with heart failure, digoxin increases myocardial contractility.

----------DOSAGE AND ADMINISTRATION----------

Toxic levels of digoxin are only slightly higher than therapeutic levels. The pharmacokinetics of digoxin are complex and dose determination should take into account patient-specific factors (age, lean body weight, renal function, etc.). (2.4)(2.5) Patients should be monitored for toxicity and therapeutic effect and doses should be adjusted, accordingly. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Oral Solution: Each 1 mL contains 0.05 mg (50 mcg) of digoxin. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to digoxin or other forms of digitalis. (4)
- Ventricular fibrillation. (4)

----------WARNINGS AND PRECAUTIONS----------

- Accessory AV Pathway: Increased risk of rapid ventricular response leading to ventricular fibrillation. (5.1)
- Sinus node disease and AV block: Digoxin use can exacerbate the condition and may cause advanced or complete heart block. (5.2)
- Misidentification of digoxin toxicity: Signs and symptoms of digoxin toxicity may be mistaken for worsening symptoms of congestive heart failure. (5.3)
- Preserved left ventricular systolic function: Patients with heart failure with preserved left ventricular ejection fraction may be more susceptible to digoxin toxicity. (5.4)
- Impaired renal function: Renal impairment results in increased digoxin exposure and requires dosage adjustments. (5.5)
- Electrolyte disorders: Toxicity is increased by hypokalemia, hypomagnesemia, and hypercalcemia. (5.6)
- Hypermetabolic states: In patients with atrial arrhythmias associated with hypermetabolic states, control of resting ventricular rate is particularly resistant to digoxin treatment. (5.8)
- The use of digoxin may result in potentially detrimental increases in coronary vascular resistance. (5.9)
- Avoid digoxin in patients with myocarditis. (5.10)

----------ADVERSE REACTIONS----------

The overall incidence of adverse reactions with digoxin has been reported as 5 to 20%, with 15 to 20% of adverse events considered serious. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse events. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Roxane Laboratories, Inc. at (800) 962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- PGP Inducers/Inhibitors: Drugs that induce or inhibit PGP have the potential to alter digoxin pharmacokinetics. (7.1)
- There are numerous drug interactions associated with digoxin. The potential for drug-drug interactions must be considered prior to and during drug therapy. See full prescribing information for a complete listing of pharmacokinetic (7.2) (12.3) and pharmacodynamic interactions (7.3).

----------USE IN SPECIFIC POPULATIONS----------

- Geriatric patients (8.5): Use caution during dose selection, taking into account renal function, and carefully monitor for side effects.
- Renal impairment (8.7): Digoxin is excreted by the kidneys. Renal function should be considered during dosage selection.
- Pregnant patients (8.1): Digoxin is classified as Pregnancy Category C, it is unknown whether use during pregnancy can cause fetal harm.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Heart Failure in Adults

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

1.2 Heart Failure in Pediatric Patients

Digoxin increases myocardial contractility in pediatric patients with heart failure.

1.3 Atrial Fibrillation in Adults

Digoxin Oral Solution, USP is indicated for the control of resting ventricular response rate in patients with chronic atrial fibrillation. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

The dose of digoxin should be based on clinical assessment but individual patient factors should be taken into consideration. Those factors are:

- Lean body weight
- Renal function
- Patient age
- Concurrent disease *[see Warnings and Precautions (6)]*
- Concomitant medication *[see Drug Interactions (7)]*

Because the pharmacokinetics of digoxin are complex, and because toxic levels of digoxin are only slightly higher than therapeutic levels, digoxin dosing can be difficult. The recommended approach is to

- estimate the patient's daily maintenance dose
- adjust the estimate to account for patient-specific factors
- choose a dosing regimen
- decide whether to initiate therapy with a loading dose
- monitor the patient for toxicity and for therapeutic effect
- adjust the dose

Dose titration may be accomplished by either of two general approaches that differ in dosage and frequency of administration, but reach the same total amount of digoxin accumulated in the body.

1. If rapid titration is considered medically appropriate, administer a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.

2. More gradual titration may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

2.2 Serum Digoxin Concentrations

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication.

Studies have shown diminished efficacy at serum levels < 0.5 ng/mL, while levels above 2 ng/mL are associated with increased toxicity without increased benefit. The inotropic effects of digoxin tend to appear at

lower concentrations than the electrophysiological effects. Based on retrospective analysis, adverse events may be higher in the upper therapeutic range.

Perform sampling of serum concentrations just before the next scheduled dose of the drug. If this is not possible, sample at least 6 hours or later after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose. The serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

When decision-making is to be guided by serum digoxin levels, the clinician must consider the possibility of reported concentrations that have been falsely elevated by endogenous digoxin-like immunoreactive substances *[see Drug Interactions (7.4)].* If the assay being used is sensitive to these substances, it may be prudent to obtain a baseline measurement before digoxin therapy is started, and correct later values by the reported baseline level.

2.3 Loading Dose

Loading doses for each age group are given in Table 1 below.

In pediatric patients, if a loading dose is needed, it can be administered with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 4- to 8-hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given as the loading dose ***[see Table 1 and 2]***.

Table 1: Estimate the Loading Dose

Age	Oral Loading Dose, mcg/kg
Premature	20 - 30
Full-Term	25 - 35
1 to 24 months	35 - 60
2 to 5 years	30 - 45
5 to 10 years	20 - 35
Over 10 years	10 - 15

More gradual attainment of digoxin levels can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in Table 2 (2.4 Estimate of Daily Maintenance Dose) can be used in calculating this dose for patients with normal renal function. Steady state will be attained after approximately 5 days in subjects with normal renal function.

2.4 Estimate of Daily Maintenance Dose

The recommended daily maintenance doses for each age group are given in Table 2 below. These recommendations assume the presence of normal renal function.

Table 2: Estimate of the Daily Maintenance Dose

Age	Daily Oral Maintenance Dose, mcg/kg/day	Dose Regimen, mcg/kg/dose
Premature	4.7 – 7.8	2.3 – 3.9 Twice daily
Full-Term	7.5 – 11.3	3.8 – 5.6 Twice daily
1 to 24 months	11.3 – 18.8	5.6 – 9.4 Twice daily
2 to 5 years	9.4 – 13.1	4.7 – 6.6 Twice daily
5 to 10 years	5.6 – 11.3	2.8 – 5.6 Once daily
Over 10 years	3.0 – 4.5	3.0 – 4.5 Once daily

Dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, dosage selection must be based upon clinical assessment and ultimately therapeutic drug level monitoring of the patient.

Divided daily dosing is recommended for pediatric patients under age 10. In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be made as shown in Tables 1 and 2. Renal clearance is further reduced in the premature infant. Beyond the immediate newborn period, pediatric patients generally require proportionally larger doses than adults on the basis of body weight or body surface area. Pediatric patients over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young pediatric patients tolerate slightly higher serum concentrations than do adults. For pediatric patients with known or suspected renal dysfunction, lower starting doses should be considered combined with frequent monitoring of digoxin levels.

NOTE: The calibrated dropper supplied with the 60 mL bottle of digoxin oral solution is not appropriate to measure doses below 0.2 mL. Doses less than 0.2 mL require appropriate methods or measuring devices designed to administer an accurate amount to the patient, such as a graduated syringe.

2.5 Adjustment of Dose

The body's handling of digoxin can be affected by many different patient-specific factors. Some of the possible effects are small, so anticipatory dose adjustment might not be required, but others should be considered before initial dosing *[see Clinical Pharmacology (12.2) and Drug Interactions (7)]*.

Both adults and pediatric patients with abnormal renal function need to have the dose of digoxin proportionally reduced. Recommended maintenance doses based upon lean body weight and renal function are listed in Table 3. Developmental changes in pediatric renal function were factored into Table 3. However, age-related and other changes in adult renal function were not.

The volume of distribution of digoxin is proportional to lean body weight and doses listed in Table 3 assume average body composition. The dose of digoxin must be reduced in patients whose lean weight is an abnormally small fraction of their total body mass because of obesity or edema.

Table 3: Usual Maintenance Dose Requirements (mcg) of Digoxin Based upon Age, Lean Body Weight and Renal Function

Corrected Ccr (mL/min per 70 kg)[b]		Dose to be given **Twice Daily** **< 10 years of age** Lean Body Weight							Dose to be given **Once Daily** **> 10 years of age and adults** Lean Body Weight							Number of Days Before Steady State Achieved
	kg	**5**	**10**	**20**	**30**	**40**	**50**	**60**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	
	lb	11	22	44	66	88	110	132	88	110	132	154	176	198	220	
10		10	20	40	60	80	100	120	80	100	120	140	160	180	200	19
20		11	23	45	68	90	113	135	90	113	135	158	180	203	225	16
30		13	25	50	75	100	125	150	100	125	150	175	200	225	250	14
40		14	28	55	83	110	138	165	110	138	165	193	220	248	275	13
50		15	30	60	90	120	150	180	120	150	180	210	240	270	300	12
60		16	33	65	98	130	163	195	130	163	195	228	260	293	325	11
70		18	35	70	105	140	175	210	140	175	210	245	280	315	350	10
80		19	38	75	113	150	188	225	150	188	225	263	300	338	375	9
90		20	40	80	120	160	200	240	160	200	240	280	320	360	400	8
100		21	43	85	128	170	213	255	170	213	255	298	340	383	425	7

a) Twice daily dosing is recommended for pediatric patients under 10 years of age. Once daily dosing is recommended for pediatric patients above 10 years of age and adults.

b) Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 – Age)/Scr. For women, this result should be multiplied by 0.85.

Note: This equation cannot be used for estimating creatinine clearance in pediatric patients. For pediatric patients, the modified Schwartz equation may be used as listed below. The formula was based on height in cm and Scr in mg/dL where k is a constant. Ccr is corrected to 1.73 m^2 body surface area. During the first year of life, the value of k is 0.33 for pre-term babies and 0.45 for term infants. The k is 0.55 for pediatric patients and adolescent girls and 0.7 for adolescent boys.

GFR (mL/min/1.73 m2) = (k x Height)/Scr

c) The doses are rounded to whole numbers.

Determination of the target dose in milliliters of Digoxin Oral Solution based on body weight is shown in Table 4. Provided is the volume required per dose, NOT per day.

Table 4: Dose in Milliliters

Target Dose in mcg/kg →		Volume to be given in mL												
		2	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**30**
Weight in kg ↓	**2**	0.08[b]	0.12[b]	0.16[b]	0.2	0.2	0.3	0.4	0.5	0.6	0.6	0.7	0.8	1.2
	3	0.12[b]	0.18[b]	0.2	0.3	0.4	0.5	0.6	0.7	0.8	1.0	1.1	1.2	1.8
	4	0.16[b]	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6	2.4
	5	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	3.0
	6	0.2	0.4	0.5	0.6	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4	3.6
	7	0.3	0.4	0.6	0.7	0.8	1.1	1.4	1.7	2.0	2.2	2.5	2.8	4.2
	8	0.3	0.5	0.6	0.8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2	4.8
	9	0.4	0.5	0.7	0.9	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6	5.4
	10	0.4	0.6	0.8	1.0	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	6.0
	11	0.4	0.7	0.9	1.1	1.3	1.8	2.2	2.6	3.1	3.5	4.0	4.4	6.6
	12	0.5	0.7	1.0	1.2	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8	7.2
	13	0.5	0.8	1.0	1.3	1.6	2.1	2.6	3.1	3.6	4.2	4.7	5.2	7.8
	14	0.6	0.8	1.1	1.4	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6	8.4
	15	0.6	0.9	1.2	1.5	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0	9.0
	20	0.8	1.2	1.6	2.0	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0	12.0
	30	1.2	1.8	2.4	3.0	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0	18.0
	40	1.6	2.4	3.2	4.0	4.8	6.4	8.0	9.6	11.2	12.8	14.4	16.0	24.0
	50	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	14.0	16.0	18	20.0	30.0
	60	2.4	3.6	4.8	6.0	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0	36.0
	70	2.8	4.2	5.6	7.0	8.4	11.2	14.0	16.8	19.6	22.4	25.2	28.0	42.0
	80	3.2	4.8	6.4	8.0	9.6	12.8	16.0	19.2	22.4	25.6	28.8	32.0	48.0
	90	3.6	5.4	7.2	9.0	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0	54.0
	100	4.0	6.0	8.0	10.0	12.0	16.0	20.0	24.0	28.0	32.0	36.0	40.0	60.0

[a] Recommended dosing regimen for pediatric patients under 10 years of age is twice daily. Recommended dosing regimen for pediatric patients over 10 years of age and adults is once daily.

[b] Use calibrated dropper for measurement. In the case of required volume less than 0.2 mL, a separate device such as a graduated syringe is recommended for adequate measurement.

On the left side of the chart, locate the patient's weight in kilograms. At the top of the chart, identify which dose in mcg/kg will be used for this patient. The block on the chart at which the two rows (weight and target dose) intersect is the milliliter amount that should be given to the patient.

The monitoring described in Section 2.2 may suggest increases or decreases in digoxin doses. Additional monitoring, and in some cases anticipatory dose adjustment, may be indicated around the time of various changes to the patient including:

- normal development through childhood;
- concomitant drug use should be considered when adjusting the estimated digoxin dose *[see Drug Interactions (7)]*;
- new co-administration of an antibiotic, especially if the patient had required high doses of digoxin in order to achieve modest serum concentrations, raising the suspicion that a substantial fraction of administered digoxin was being destroyed by colonic bacteria; and
- changes in renal function [see *Table 3: Usual Maintenance Dose Requirements (mcg) of Digoxin* above].

3 DOSAGE FORMS AND STRENGTHS

Each 1 mL of clear, colorless Digoxin Oral Solution contains 0.05 mg (50 mcg).

The Digoxin Oral Solution bottles are to be used with the graduated droppers provided in the carton. Starting at 0.2 mL, this 1 mL dropper is marked in divisions of 0.1 mL, corresponding to 5 mcg or 0.005 mg of digoxin.

NOTE: The calibrated dropper supplied with the 60 mL bottle of Digoxin Oral Solution is not appropriate to measure doses below 0.2 mL. Doses less than 0.2 mL require appropriate methods or measuring devices designed to administer an accurate amount to the patient, such as a graduated syringe.

4 CONTRAINDICATIONS

Allergy to digoxin is rare. Digoxin is contraindicated in patients with a known hypersensitivity to digoxin or other forms of digitalis. Digitalis glycosides, such as digoxin, are contraindicated in ventricular fibrillation.

5 WARNINGS AND PRECAUTIONS

5.1 Use in Patients with Accessory AV Pathway (Wolff-Parkinson-White Syndrome)

Patients with Wolff-Parkinson-White syndrome who develop atrial fibrillation are at high risk of ventricular fibrillation. Treatment of these patients with digoxin leads to greater slowing of conduction in the atrioventricular node than in accessory pathways, and the risks of rapid ventricular response leading to ventricular fibrillation are thereby increased.

5.2 Use in Patients with Sinus Node Disease and AV Block

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. Digoxin may cause severe sinus bradycardia or sinoatrial block particularly in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

5.3 Misidentification of Digoxin Toxicity

Some signs and symptoms (anorexia, nausea, vomiting, and certain arrhythmias) can equally result from digoxin toxicity as from congestive heart failure. Misidentification of their etiology might lead the clinician to continue or increase digoxin dosing, when dosing should actually be suspended. When the etiology of these signs and symptoms is not obvious, measurement of serum digoxin levels may be helpful.

5.4 Use in Patients with Preserved Left Ventricular Systolic Function

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may not benefit from digoxin treatment and may be particularly susceptible to adverse reactions when they are treated with digoxin.

In patients with hypertrophic cardiomyopathy (formerly called idiopathic hypertrophic subaortic stenosis), the positive inotropic effect of digoxin leads to an increased subvalvular outflow gradient and therefore, may compromise cardiac output. Digoxin is rarely beneficial in patients with this condition.

Chronic constrictive pericarditis is not generally associated with any inotropic defect, so heart failure of this etiology is unlikely to respond to treatment with digoxin. By slowing the resting heart rate, digoxin may actually decrease cardiac output in these patients.

Digoxin as an inotropic agent is of limited value in patients with restrictive cardiomyopathies, although it has been used for ventricular rate control in the subgroup of patients with atrial fibrillation. In addition, patients with amyloid heart disease may be more susceptible to toxicity from digoxin at therapeutic levels because of an increased binding of digoxin to extracellular amyloid fibrils.

5.5 Use in Patients with Impaired Renal Function

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin *[see Dosage and Administration (2.4)]*. Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

5.6 Use in Patients with Electrolyte Disorders

In patients with hypokalemia or hypomagnesemia, toxicity may occur at concentrations within therapeutic range because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Serum potassium levels should be carefully monitored when digoxin is given to patients at high risk of hypokalemia (*e.g.*, those receiving diuretics, corticosteroids, or other drugs that commonly lead to potassium loss; those with gastrointestinal losses through diarrhea, vomiting, or nasogastric suction; or those with potassium-losing endocrinopathies or nephropathies).

Digoxin toxicity is also more likely in the presence of hypomagnesemia. Hypomagnesemia is common in most of the same conditions in which hypokalemia appears. Most notably, it is commonly seen in alcoholics and in patients with diabetes mellitus or hypercalcemia.

Because digoxin's therapeutic and toxic effects are all largely mediated by intracellular calcium distribution, they are affected by abnormalities in serum calcium levels. Hypercalcemia increases the risk of digoxin toxicity, while digoxin may be therapeutically ineffective in the presence of hypocalcemia.

5.7 Use During Electrical Cardioversion

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

5.8 Use in Thyroid Disorders and Hypermetabolic States

Hypothyrodism may reduce the requirements for digoxin. Heart failure and atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition.

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

5.9 Use in Patients with Acute Myocardial Infarction

In patients with acute myocardial infarction, particularly if they have ongoing ischemia, the use of inotropic drugs, such as digoxin, may result in undesirable increases in myocardial oxygen demand and ischemia. Moreover, the use of digoxin may result in potentially detrimental increases in coronary vascular resistance mediated through alpha adrenergic receptor stimulation.

5.10 Use in Patients with Myocarditis

Digoxin can precipitate vasoconstriction and may promote production of pro-inflammatory cytokines. Therefore, avoid digoxin in patients with myocarditis.

5.11 ECG Changes During Exercise

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing that may be indistinguishable from those of ischemia. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity. Digoxin does not significantly decrease heart rate during exercise.

5.12 Laboratory Tests

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting.

Assays of serum digoxin levels are described elsewhere *[see Drug Interactions (7.4)]*, as is their use in patient monitoring *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

The frequency and severity of adverse reactions to digoxin when taken orally depend on the dose and the patient's underlying disease or concomitant therapies *[see Warnings and Precautions (6) and Drug Interactions (7)].* The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (1 to 4% of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. Adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

6.1 Cardiac

In adults, high doses of digoxin may produce a variety of electrocardiographic changes and rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multifocal ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable.

In pediatric patients, the use of digoxin may produce arrhythmia. The most common are conduction disturbances or supraventricular tachycarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmias or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

6.2 Gastrointestinal

Anorexia, nausea, vomiting and diarrhea may be early symptoms of digoxin toxicity. However, uncontrolled heart failure may also produce such symptoms. The use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

6.3 CNS and Special Senses

Digoxin can produce visual disturbances (blurred vision, green-yellow color disturbances, halo effect), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

6.4 Other

Gynecomastia has been reported following the prolonged use of digoxin. Thrombocytopenia, maculopapular rash and other skin reactions have been observed.

7 DRUG INTERACTIONS

7.1 P-Glycoprotein (PGP) Inducers/Inhibitors

Digoxin is a substrate for P-glycoprotein, at the level of intestinal absorption, renal tubular section and biliary-intestinal secretion. Therefore, drugs that induce/inhibit P-glycoprotein have the potential to alter digoxin pharmacokinetics.

7.2 Pharmacokinetic Drug Interactions on Serum Digoxin Levels in Adults

Digoxin concentrations increased > 50%			
	Digoxin Serum Concentration Increase	Digoxin AUC Increase	**Recommendations**
Amiodarone	70%	NA	Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 30% to 50% and continue monitoring.
Captopril	58%	39%	
Nitrendipine	57%	15%	
Propafenone	35-85%	NA	
Quinidine	100%	NA	
Ranolazine	87%	88%	
Ritonavir	NA	86%	
Verapamil	50-75%	NA	
Digoxin concentrations increased < 50%			
Carvedilol	16%	14%	Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 15% to 30% and continue monitoring.
Diltiazem	20%	NA	
Nifedipine	45%	NA	
Rabeprazole	29%	19%	
Telmisartan	20%	NA	
Digoxin concentrations increased, but magnitude is unclear			
Alprazolam, Azithromycin, Clarithromycin, Cyclosporine, Diclofenac, Diphenoxylate, Epoprostenol, Erythromycin, Esomeprazole, Indomethacin, Itraconazole, Ketoconazole, Lansoprazole, Metformin, Omeprazole, Propantheline, Spironolactone, Tetracycline			Measure serum digoxin concentrations before initiating concomitant drugs. Continue monitoring and reduce digoxin dose as necessary.
Digoxin concentrations decreased			

Acarbose, Activated Charcoal, Albuterol, Antacids, Anti-cancer drugs, Cholestyramine, Colestipol, Exenatide, Kaolin-pectin, Meals High in Bran, Metoclpramide, Miglitol, Neomycin, Rifampin, Salbutamol, St. John's Wort, Sucralfate, Sulfasalazine	Measure serum digoxin concentrations before initiating concomitant drugs. Continue monitoring and increase digoxin dose by approximately 20% to 40% as necessary.
No significant Digoxin concentrations changes	
Please refer to section 12.3 for a complete list of drugs which were studied but reported no significant changes on digoxin exposure.	No additional actions are required.

NA – Not available/reported

7.3 Pharmacodynamic Drug Interactions

Antiarrthymics	Dofetilide	Concomitant administration with digoxin was associated with a higher rate of torsade de pointes.
	Moricizine	Reported to increase PR interval and QRS duration. There are reports of first degree atrioventricular block or bundle branch block developing with digitalis administration. The known effects of moricizine on calcium conductance may explain the effects on atrioventricular node conduction.
	Sotalol	Proarrhythmic events were more common in patients receiving sotalol and digoxin than on either alone; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digoxin.
Parathyroid Hormone Analog	Teriparatide	Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Teriparatide transiently increases serum calcium.
Thyroid Supplement	Thyroid	Treatment of hypothyroidism in patients taking digoxin may increase the dose requirements of digoxin.
Sympathomimetics	Epinepherine Norepinephrine Dopamine	Can increase the risk of cardiac arrhythmias.
Neuromuscular Blocking Agents	Succinylcholine	May cause sudden extrusion of potassium from muscle cells causing arrhythmias in patients taking digoxin.
Supplements	Calcium	If administered rapidly by intravenous route, can produce serious arrhythmias in digitalized patients.
Beta-adrenergic blockers and calcium channel blockers	Additive effects on AV node conduction can result in complete heart block.	

7.4 Drug-Laboratory Test Interaction

Endogenous substances of unknown composition (digoxin-like immunoreactive substances, DLIS) can interfere with standard radioimmunoassays for digoxin. The interference most often causes results to be falsely positive or falsely elevated, but sometimes it causes results to be falsely reduced. Some assays are more subject to these failings than others. Several LC/MS/MS methods are available that may provide less susceptibility to DLIS interference. DLIS are present in up to half of all neonates and in varying percentages of pregnant women, patients with hypertrophic cardiomyopathy, patients with renal or hepatic dysfunction, and other patients who are volume-expanded for any reason. The measured levels of DLIS (as digoxin equivalents)

are usually low (0.2 to 0.4 ng/mL), but sometimes they reach levels that would be considered therapeutic or even toxic.

In some assays, spironolactone, canrenone and potassium canrenoate may be falsely detected as digoxin, at levels up to 0.5 ng/mL. Some traditional Chinese and Ayurvedic medicine substances like Chan Su, Siberian Ginseng, Asian Ginseng, Ashwagandha or Dashen, can cause similar interference.

Spironolactone and DLIS are much more extensively protein-bound than digoxin. As a result, assays of free digoxin levels in protein-free ultrafiltrate (which tend to be about 25% less than total levels, consistent with the usual extent of protein binding) are less affected by spironolactone or DLIS. It should be noted that ultrafiltration does not solve all interference problems with alternative medicines. The use of an LC/MS/MS method may be the better option according to the good results it provides, especially in term of specificity and limit of quantization.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects (Pregnancy Category C)

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Digoxin should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

There is not enough data from clinical trials to determine the safety and efficacy of digoxin during labor and delivery.

8.3 Nursing Mothers

Digoxin levels in human milk are lower than those in maternal serum. The estimated exposure that a nursing infant would be expected to receive via breastfeeding would be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

8.4 Pediatric Use

Digoxin increases myocardial contractility in pediatric patients with congestive heart failure. There are no clinical efficacy studies demonstrating benefit in pediatric patients with heart failure. There are no controlled randomized studies of digoxin in pediatric patients with atrial tachyarrhythmias *[see Clinical Studies (14.2)].*

8.5 Geriatric Use

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function *[see Dosage and Administration (2.4)].*

8.6 Gender

No clinically significant gender differences in digoxin pharmacokinetics have been reported.

8.7 Renal Impairment

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. Table 3 provides the usual daily maintenance dose requirements of solution based on creatinine clearance (per 70 kg or per 1.73 m^2) *[see Dosage and Administration (2.4)].*

For pediatric patients with known or suspected renal dysfunction, lower starting doses should be considered combined with frequent monitoring of digoxin levels.

8.8 Hepatic Impairment

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

8.9 Thyroid Status

In hyperthyroidism, lower serum digoxin concentrations have been reported because of decreased absorption. Hypothyroid patients may require smaller doses of digoxin.

8.10 Race

Race differences in digoxin pharmacokinetics have not been formally studied, but are not expected.

8.11 Malabsorption

The absorption of digoxin is reduced in some malabsorption conditions such as chronic diarrhea.

10 OVERDOSAGE

10.1 Clinical Manifestations

In adults, the signs and symptoms of toxicity are similar to those described in *Adverse Reactions (6)* but may be more frequent and severe. The most common signs and symptoms of digoxin toxicity are nausea, vomiting, anorexia, and fatigue that occur in 30 to 70% of patients who are overdosed. Extremely high serum concentrations produce hyperkalemia especially in patients with impaired renal function. Almost every type of cardiac arrhythmia has been associated with digoxin overdose and multiple rhythm disturbances in the same patient are common. Peak cardiac effects occur 3 to 6 hours following ingestion and may persist for 24 hours or longer. Arrhythmias that are considered more characteristic of digoxin toxicity are new-onset Mobitz type 1 A-V block, accelerated junctional rhythms, non-paroxysmal atrial tachycardia with A-V block, and bi-directional ventricular tachycardia. Cardiac arrest from asystole or ventricular fibrillation is usually fatal.

Digoxin toxicity is related to serum concentration. As serum levels increase above 1.2 ng/mL, there is a potential for increase in adverse events. The effect on adverse events is enhanced by lower potassium levels. In adults with heart disease, clinical observations suggest that an overdose of digoxin of 10 to 15 mg results in death of half of patients. A dose above 25 mg ingested by an adult without heart disease appeared to be uniformly fatal if no Digoxin Immune Fab (DIGIBIND®, DIGIFAB®) was administered.

In pediatric patients, signs and symptoms of toxicity can occur during or shortly after the dose of digoxin. Frequent non-cardiac effects are similar to those observed in adults although nausea and vomiting are not seen frequently in infants and small pediatric patients. Other reported manifestations of overdose are weight loss in older age groups, failure to thrive in infants, abdominal pain caused by mesenteric artery ischemia, drowsiness, and behavioral disturbances including psychotic episodes. Arrhythmias and combinations of arrhythmias that occur in adult patients can also occur in pediatric patients although sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen less frequently in pediatric patients. Pediatric patients are more likely to develop A-V conduction disturbances, or sinus bradycardia. Any arrhythmia in a child treated with digoxin should be considered related to digoxin until otherwise ruled out. In pediatric patients aged 1 to 3 years without heart disease, clinical observations suggest that an overdose of digoxin of 6 to 10 mg would result in death of half of the patients. In the same population, a dose above 10 mg resulted in death if no Digoxin Immune Fab (DIGIBIND®, DIGIFAB®) was administered.

10.2 Management of Toxicity

Chronic Overdose

If there is suspicion of toxicity, digoxin should be discontinued and the patient placed on a cardiac monitor. Contributing factors such as electrolyte abnormalities, thyroid dysfunction, and concomitant medications should be corrected *[see Dosage and Administration (2.5)]*. Hypokalemia should be corrected by administering potassium so that serum potassium is maintained between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and serum potassium concentration is low, potassium may be administered cautiously by the intravenous route. The electrocardiogram should be

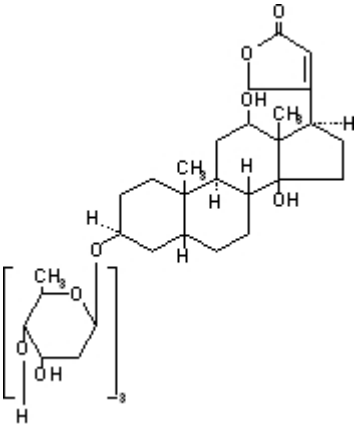
monitored for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. Potassium salts should be avoided in patients with bradycardia or heart block. Symptomatic arrhythmias may be treated with Digoxin Immune Fab (DIGIBIND®, DIGIFAB®).

Acute Overdose

Patients who have intentionally or accidently ingested massive doses of digoxin should receive activated charcoal orally or by nasogastric tube regardless of the time since ingestion since digoxin recirculates to the intestine by enterohepatic circulation. In addition to cardiac monitoring, digoxin should be temporarily discontinued until the adverse reaction resolves. Factors that may be contributing to the adverse reactions should also be corrected *[see Warnings and Precautions (5)]*. In particular, hypokalemia and hypomagnesemia should be corrected. Digoxin is not effectively removed from the body by dialysis because of its large extravascular volume of distribution. Life threatening arrhythmias (ventricular tachycardia, ventricular fibrillation, high degree A-V block, bradyarrhythma, sinus arrest) or hyperkalemia requires administration of Digoxin Immune Fab (DIGIBIND®, DIGIFAB®). Digoxin Immune Fab has been shown to be 80-90% effective in reversing signs and symptoms of digoxin toxicity. Bradycardia and heart block caused by digoxin are parasympathetically mediated and respond to atropine. A temporary cardiac pacemaker may also be used. Ventricular arrhythmias may respond to lidocaine or phenytoin. When a large amount of digoxin has been ingested, especially in patients with impaired renal function, hyperkalemia may be present due to release of potassium from skeletal muscle. In this case, treatment with Digoxin Immune Fab (DIGIBIND®, DIGIFAB®) is indicated; an initial treatment with glucose and insulin may be needed if the hyperkalemia is life-threatening. Once the adverse reaction has resolved, therapy with digoxin may be reinstituted following a careful reassessment of dose.

11 DESCRIPTION

Digoxin is one of the cardiac glycosides, a closely-related group of plant-derived drugs with shared pharmacological effects. The term "digitalis" is used to designate the whole group. Digoxin is extracted from the leaves of the common foxglove, *Digitalis lanata*. Like each of the other cardiac glycosides, digoxin consists of a polycyclic core and a sugar side chain. Digoxin's chemical name is 3β-[*0*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*0*-2, 6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2, 6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β, 14-dihydroxy-5β-card-20(22)-enolide; its structural formula is:



Its molecular formula is $C_{41}H_{64}O_{14}$, and its molecular weight is 780.95. Digoxin is practically insoluble in water and in ether, slightly soluble in 50% ethanol and in chloroform, and freely soluble in pyridine. Digoxin powder consists of odorless white crystals.

Digoxin Oral Solution, USP is formulated for oral administration, and each mL contains 50 mcg (0.05 mg digoxin). The lime-flavored solution contains the following inactive ingredients: alcohol 10% (by volume at 60°F), glycerin, lime (imitation), methylparaben 0.1%, propylparaben 0.02%, purified water, sodium citrate, and sorbitol solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

All of digoxin's actions are mediated through its effects on NaK–ATPase. This enzyme, the "sodium pump," is responsible for maintaining the intracellular milieu throughout the body by moving sodium ions out of and potassium ions into cells. By inhibiting NaK–ATPase, digoxin

- causes increased availability of intracellular calcium in the myocardium and conduction system, with consequent increased inotropy, increased automaticity, and reduced conduction velocity;
- indirectly causes parasympathetic stimulation of the autonomic nervous system, with consequent effects on the sino-atrial (SA) and atrioventricular (AV) nodes;
- reduces catecholamine reuptake at nerve terminals, rendering blood vessels more sensitive to endogenous or exogenous catecholamines;
- increases baroreceptor sensitization, with consequent increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increment in mean arterial pressure;
- increases (at higher concentrations) sympathetic outflow from the central nervous system (CNS) to both cardiac and peripheral sympathetic nerves; and
- allows (at higher concentrations) progressive efflux of intracellular potassium, with consequent increase in serum potassium levels.

The cardiologic consequences of these direct and indirect effects are an increase in the force and velocity of myocardial systolic contraction (positive inotropic action), a slowing of the heart rate (negative chronotropic effect), decreased conduction velocity through the AV node, and a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect).

12.2 Pharmacodynamics

Short- and long-term treatment with digoxin slows heart rate, increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

12.3 Pharmacokinetics

Absorption

Following oral administration, peak serum concentrations of digoxin occur at 30 to 90 minutes. In pediatric patients and in adult volunteers, absolute bioavailability of digoxin from the solution formulation is 70 to 85%, similar to that seen (in adults) with standard tablets (60 to 80%). When the solution is taken after meals, the peak serum concentrations increase by 20% and the total amount of digoxin absorbed increases by 43%, but the rate of digoxin absorption is unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Digoxin absorption may also be affected by various concomitant therapy modulating gastric pH and P-glycoprotein *[see Drug Interactions (7)]*.

Comparisons of the systemic availability and equivalent doses for preparations of digoxin are shown in Table 5.

Table 5: Comparisons of the Systemic Availability and Equivalent Doses for Preparations of Digoxin

Product	Absolute Bioavailability	Equivalent Doses (mcg)[a] Among Dosage Forms			
Tablets	60-80%	62.5	125	250	500
Solution	70-85%	62.5	125	250	500
Capsules	90-100%	50	100	200	400
Injection/IV	100%	50	100	200	400

a) For example, 125 mcg tablets equivalent to 125 mcg solution equivalent to 100 mcg capsules equivalent to 100 mcg injection/IV.

In some patients, orally administered digoxin is converted to inactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggested that one in ten patients treated with digoxin will degrade 40% or more of the ingested dose. As a result, certain antibiotics may increase the absorption of digoxin in such

patients. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Distribution

Following drug administration, a 6- to 8-hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its sites of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects *[see Dosage and Administration (2.2)].*

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

Metabolism

Sixteen percent of digoxin is metabolized. The end metabolites include 3-β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates. The metabolism of digoxin is not dependent on cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion

Elimination of digoxin is predominantly renal, although in adult volunteers about a quarter of serum digoxin is eliminated through the intestine, excreted in bile or secreted directly into the lumen by P-glycoprotein. Elimination of digoxin follows first order kinetics.

Following intravenous administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate.

The serum half-life of digoxin in pediatric patients is reported to be 18 to 36 hours, and in adults it is typically 36 to 48 hours. The half-life in anuric patients is prolonged to 3.5 to 5 days.

Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or cardiopulmonary bypass because most of the drug is bound to tissue.

Drug-drug Interactions

Based on literature reports no significant changes in digoxin exposure was reported when digoxin was co-administered with the following drugs: alfuzosin, aliskiren, amlodipine, aprepitant, argatroban, aspirin, atorvastatin, benazepril, bisoprolol, black cohosh, bosentan, candesartan, citalopram, clopidogrel, colesevelam, dipyridamole, disopyramide, donepezil, doxazosin, dutasteride, echinacea, enalapril, eprosartan, ertapenem, escitalopram, esmolol, ezetimibe, famciclovir, felodipine, finasteride, flecainide, fluvastatin, fondaparinux, galantamine, gemifloxacin, grapefruit juice, irbesartan, isradipine, ketorlac, levetiracetam, levofloxacin, lisinopril, losartan, lovastatin, meloxicam, mexilitine, midazolam, milk thistle, moexipril, montelukast, moxifloxacin, mycophenolate, nateglinide, nesiritide, nicardipine, nisoldipine, olmesartan, orlistat, pantoprazole, paroxetine, perindopril, pioglitazone, pravastatin, prazosin, procainamide, quinapril, raloxifene, ramipril, repaglinide, rivastigmine, rofecoxib, ropinirole, rosiglitazone, rosuvastatin, sertraline, sevelamer, simvastatin, sirolimus, solifenacin, tamsulosin, tegaserod, terbinafine, tiagabine, ticlopidine, tigecycline, topiramate, torsemide, tramadol, trandolapril, triamterene, trospium, trovafloxacin, valacyclovir, valsartan, varenicline, voriconazole, zaleplon, and zolpidem.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Chronic Heart Failure

Two small12-week, double-blind, randomized trials compared digoxin to placebo in adult patients with chronic congestive heart failure, New York Heart Association Class II or III. The enrolled patients had all been receiving digoxin before the trials, but this was withdrawn before randomization. They continued to receive diuretics and (in the larger trial) ACE inhibitors. The trials enrolled 178 and 88 patients, respectively. In each of these trials, randomization to digoxin was associated with better preservation of exercise capacity and with reduced need of failure-related hospitalization, emergency care, and concomitant heart-failure therapy. NYHA class and patients' global assessments were also improved, although this effect achieved statistical significance only in the larger of the two studies.

The Digitalis Investigation Group (DIG) main trial was a 37-week, multicenter, randomized, double-blind mortality study comparing digoxin to placebo in 6800 adult patients with heart failure and left ventricular ejection fraction ≤0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving a concomitant ACE inhibitor (94%) and diuretics (82%). As in the smaller trials described above, patients who had been receiving open-label digoxin were withdrawn from this treatment before randomization. Randomization to digoxin was again associated with a significant reduction in the incidence of hospitalization, whether scored as number of hospitalizations for heart failure (relative risk 75%), risk of having at least one such hospitalization during the trial (RR 72%), or number of hospitalizations for any cause (RR 94%). On the other hand, randomization to digoxin had no apparent effect on mortality (RR 99%, with confidence limits of 91 to 107%).

14.2 Atrial Fibrillation

Digoxin has also been studied as a means of controlling the ventricular response to chronic atrial fibrillation in adults. Digoxin reduced the resting heart rate, but not the heart rate during exercise.

In 3 different randomized, double-blind trials that included a total of 315 adult patients, digoxin was compared to placebo for the conversion of recent-onset atrial fibrillation to sinus rhythm. Conversion was equally likely, and equally rapid, in the digoxin and placebo groups. In a randomized 120-patient trial comparing digoxin, sotalol, and amiodarone, patients randomized to digoxin had the lowest incidence of conversion to sinus rhythm, and the least satisfactory rate control when conversion did not occur.

In at least one study, digoxin was studied as a means of delaying reversion to atrial fibrillation in adult patients with frequent recurrence of this arrhythmia. This was a randomized, double-blind, 43-patient crossover study. Digoxin increased the mean time between symptomatic recurrent episodes by 54%, but had no effect on the frequency of fibrillatory episodes seen during continuous electrocardiographic monitoring.

No controlled randomized study of digoxin in pediatric patients with atrial tachyarrhythmias has been done.

14.3 Atrial Flutter

There are no reports of controlled trials of digoxin for conversion of atrial flutter, rate control during atrial flutter, or reduction of the frequency of recurrence of atrial flutter in adults.

14.4 Supraventricular Tachycardia

There are no reports of controlled trials of digoxin for conversion of supraventricular tachycardia (SVT), rate control during SVT, or reduction of the frequency of recurrence of SVT in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

Digoxin Oral Solution, USP 0.05 mg (50 mcg) per 1 mL is a clear, colorless solution available in one strength as follows:

0.05 mg per 1 mL Oral Solution

NDC 0054-0057-46: Bottle of 60 mL with a calibrated dropper

Storage

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

17 PATIENT COUNSELING INFORMATION

Patients receiving digoxin should be given the following instructions by the physician.

- Advise patients that digoxin is a cardiac glycoside used to treat heart failure and heart arrhythmias. Digoxin helps the heart beat more efficiently in adults and pediatric patients and decreases the heart rate at rest during abnormal rhythms in adults.
- Instruct patients to take this medication as directed by their physician. The dose of digoxin should not be adjusted without consulting with a physician or other healthcare professional.
- Advise patients that many drugs can interact with digoxin. Patients should be instructed to inform their doctor and pharmacist if they are taking any over the counter medications, including herbal medication, or are started on a new prescription.
- The patient should be made aware that blood tests will be necessary to ensure that their digoxin dose is appropriate for them.
- Advise patients to contact their doctor or a health care professional if they experience nausea, vomiting, persistent diarrhea, confusion, weakness, or visual disturbances (including blurred vision, green-yellow color disturbances, halo effect) as these could be signs that the dose of digoxin may be too high.
- Advise parents or caregivers that the symptoms of having too high digoxin doses may be difficult to recognize in infants and pediatric patients. Symptoms such as weight loss, failure to thrive in infants, abdominal pain, and behavioral disturbances may be indications of digoxin toxicity.
- Suggest to the patient to monitor and record their heart rate and blood pressure daily.
- Instruct patients to use the calibrated dropper to measure their digoxin dose and to avoid less precise measuring tools, such as teaspoons. For doses less than 0.2 mL, another measuring syringe should be provided to the patient for accurate dosing, since the provided calibrated dropper is not appropriate to measure doses less than 0.2 mL.
- Instruct women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiation or continuing therapy with digoxin.

Roxane Laboratories, Inc.
Columbus, Ohio 43216

10001143/06 **Revised September 2011**

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/s/

MARY R SOUTHWORTH
09/26/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021648Orig1s004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review
Labeling Supplement

NDA:	21648
PRODUCT (Generic Name):	Digoxin
PRODUCT (Brand Name):	Digoxin Oral Solution
DOSAGE FORM:	Oral Solution
DOSAGE STRENGTH:	0.05 mg/mL, 60 mL/Bottle
INDICATION:	treatment of mild to moderate heart failure and for the control of ventricular response rate in patients with chronic atrial fibrillation
SUBMISSION DATE:	10/5/10
SPONSOR:	Roxane Laboratories, Inc
REVIEWER:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Rajanikanth Madabushi, PhD
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Digoxin is one of the cardiac glycosides whose actions are mediated through its effects on NaK–ATPase. It is indicated for the treatment of heart failure and atrial fibrillation. Digoxin has been in clinical use long before its first official approval by FDA in 1982 as an oral capsule, and different strengths and formulations have been developed and approved since then.

In June 2010, the sponsor Roxane Laboratories, Inc was asked by the Agency to update the label of DIGOXIN ELIXIR which was approved in 2004, to the new format. The sponsor subsequently in October 2010 submitted another new label with changes. The sponsor applied the new information from the most updated digoxin label, Lanoxin, which was approved in February 2010 and based on published literatures for the proposed changes to reflect the current view of digoxin.

In this labeling supplement, the clinical pharmacology related changes in DOSAGE AND ADMINISTRATION, Section 2.1, 2.2, 2.3, 2.4; WARNINGS AND PRECAUTIONS, Section 5.5; DRUG INTERACTIONS, Section 7.1, 7.2, 7.3, 7.4; USE IN SPECIFIC POPULATIONS, Section 8.3, 8.5, 8.10 and CLINICAL PHARMACOLOGY, Section 12.3 were reviewed. Among the changes incorporated directly from the Lanoxin labeling, no further review for these data was performed. However, the changes specifically for section 7.1, 7.2 and 7.4 were based on publications which were reviewed by The Office of Clinical Pharmacology (OCP). Recommendations for the sponsor's proposal and additional key labeling changes proposed by OCP were provided below.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this submission and found this sNDA to be acceptable provided that satisfactory agreement is reached between the sponsor and the division regarding the language in the labeling. Detailed recommendations from clinical pharmacology perspective for the labeling are included in the Labeling Section (Section 3) of this review. A brief summary of the key labeling changes recommended are listed below:

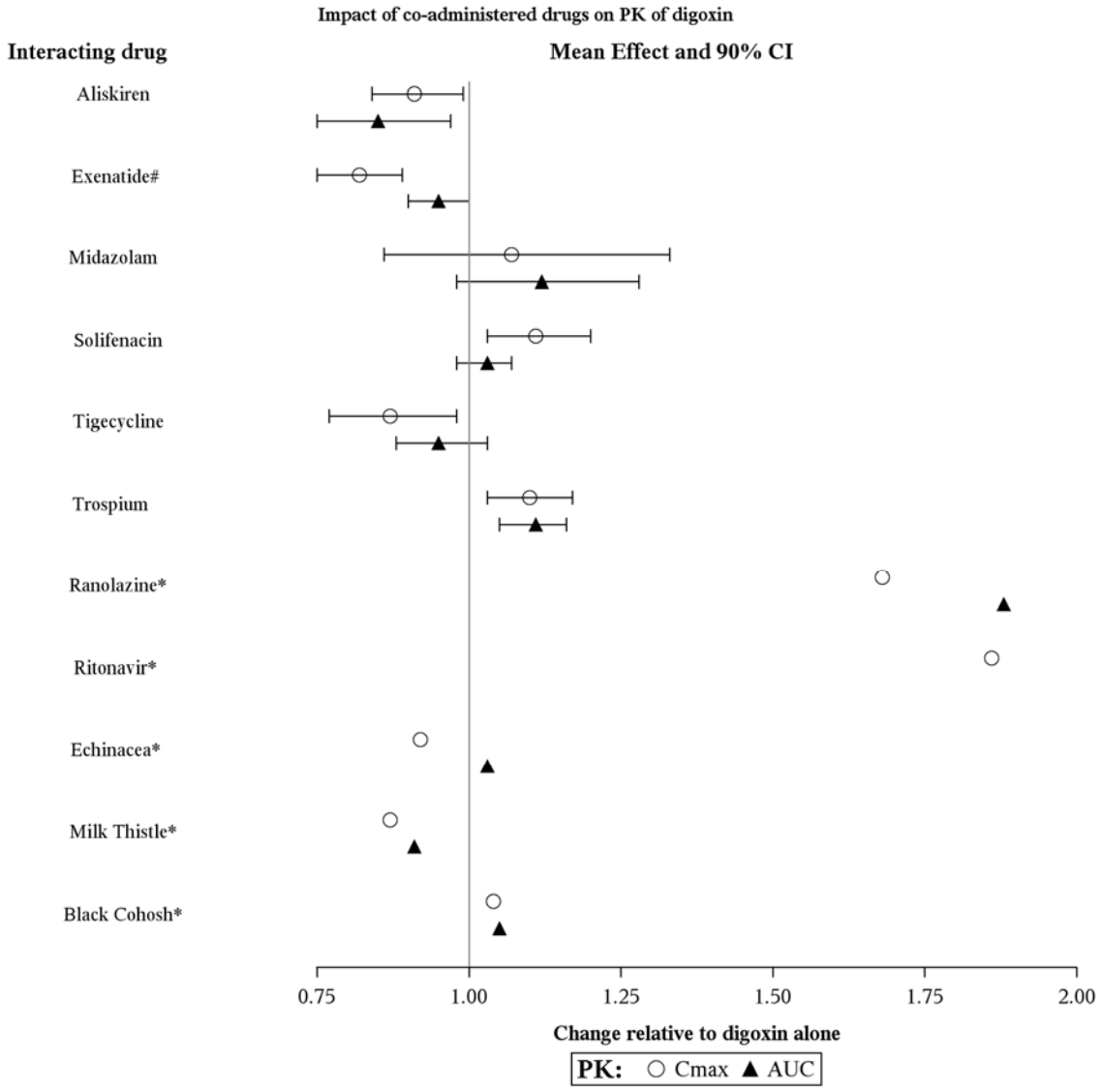
- Estimates of loading dose for digoxin are derived for the Oral Solution based on the Digoxin IV label after accounting for the bioavailabilty of 80%.
- Estimates for the daily maintenance dose (once daily and twice daily) for the Oral Solution are derived from the Digoxin IV label after accounting for the bioavailability of 80%. This allowed for proposing dosing instruction to pediatric patients for Oral Solution formulation.
- Estimates for the dose adjustment for renal impaired patients are extended to include recommended doses for renal impaired pediatric patients.
- A modified Schwartz equation is proposed for dose adjustment based on renal function in pediatric patients.
- The reporting of the drug interactions for digoxin is made concise by the use of a table. Clarity for this information is provided in the form of classifying drugs

based on the magnitude of the pharmacokinetic interaction and the required digoxin dose adjustment is proposed.

2.0 Clinical Pharmacology Summary

2.1 Summary of DDI studies:

- A summary of the drug interactions submitted with the current submission is presented in the Forest Plot below:



#Tmax of digoxin is shifted fron 1.5 h to 4 h with exanetide
** 90% CI data not available.*

3 LABELING RECOMMENDATIONS

Only Sections contain clinical pharmacology related changes are provided. New language proposed is marked in **Blue**. Deletions are shown as ~~**strikethroughs**~~. The rationale supporting the reviewer's edits are provided below the specific edits as ***Reviewer's Comments***.

2.1 General Dosing Considerations

The dose of digoxin should be based on clinical assessment but individual patient factors should be taken into consideration. Those factors are:

- Lean body weight
- Renal function
- Patient age
- Concurrent disease [*see* WARNINGS AND PRECAUTIONS(6.0)]
- Concomitant medication [*see* DRUG INTERACTIONS (7.0)]

Because the pharmacokinetics of digoxin are complex, and because toxic levels of digoxin are only slightly higher than therapeutic levels, digoxin dosing can be difficult. The recommended approach is to

- estimate the patient's daily maintenance dose
- adjust the estimate to account for patient-specific factors
- choose a dosing regimen
- decide whether to initiate therapy with a loading dose
- monitor the patient for toxicity and for therapeutic effect adjust the dose

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

1. If rapid titration is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.

2. More gradual titration may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Reviewer's Comments:
As the loading dose is newly added in this label, the language above was obtained from the Lanoxin Injection Pediatric Label to provide a transition and explain the dose titration can be done by 2 different approaches.

2.3 Loading Dose:

Loading doses for each age group are given in Table 1 below.

In pediatric patients, if a loading dose is needed, it can be administered with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 4- to 8-hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given as the loading dose **(SEE TABLE 1 and 2)**.

Table 1: Estimate the Daily Loading Dose

Age	Daily Oral Loading Dose, mcg/kg/day
Premature	20 - 30
Full-Term	25 - 35
1 to 24 months	35 - 60
2 to 5 years	30 - 45
5 to 10 years	20 - 35
Over 10 years	10 - 15

More gradual attainment of digoxin levels can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in Table 2 (2.4 Estimate of Daily Maintenance Dose) can be used in calculating this dose for patients with normal renal function. Steady state will be attained after approximately 5 days in subjects with normal renal function.

Reviewer's Comment:
A new section, 2.3 Loading dose, is added with the proposed dosing regimen for Oral Solution (table above) derived from Lanoxin Injection Pediatrics label. The doses were calculated by multiplying a factor of 1.25 from IV digitalizing doses based on the approximately 80% absolute bioavailability of Elixir. Rounded numbers are provided in the label (see appendix for the actual calculated doses).

2.4 Estimate of Daily Maintenance Dose:

The recommended daily maintenance doses for each age group are given in Table 2 below. These recommendations assume the presence of normal renal function.

Table 2: Estimate of the Daily Maintenance Dose

Age	Daily Oral Maintenance Dose, mcg/kg/day	Oral Maintenance Dose for Twice or Once Daily Dose Regimen, mcg/kg/dose
Premature	4.7 – 7.8	2.3 – 3.9 Twice daily
Full-Term	7.5 – 11.3	3.8 – 5.6 Twice daily
1 to 24 months	11.3 – 18.8	5.6 – 9.4 Twice daily
2 to 5 years	9.4 – 13.1	4.7 – 6.6 Twice daily
5 to 10 years	5.6 – 11.3	2.8 – 5.6 Twice daily
Over 10 years	3.0 – 4.5	3.0 – 4.5 Once daily

Reviewer's Comment:
The old table for Daily Maintenance Doses was replaced to include age less than 2 years as shown above. The maintenance oral dose was calculated by a factor of 0.25 of the oral loading dose for premature and 0.3 for full-term to age less than 10 years old. This calculation is based on the recommendation of maintenance dose in the Lanoxin Injection Pediatrics Label. Rounded numbers are provided in the label (see appendix for the actual calculated doses). Estimate of Daily Maintenance Dose for twice daily for pediatric patients under 10 years of age are also provided.

2.5 Adjustment of Dose

Table 3: Usual Maintenance Dose Requirements (mcg) of digoxin based upon age, lean body weight and renal function.

Table 3: Usual Maintenance Dose Requirements (mcg) of Digoxin

Corrected Ccr (mL/min per 70 kg) [b]	Dose to be given **Twice Daily** < 10 years of age							Dose to be given **Once Daily** > 10 years of age and adults							Number of Days Before Steady State Achieved
	Lean Body Weight							Lean Body Weight							
	kg	5	10	20	30	40	50	60	40	50	60	70	80	90	100	
	lb	11	22	44	66	88	110	132	88	110	132	154	176	198	220	
10		10	20	40	60	80	100	120	80	100	120	140	160	180	200	19
20		11	23	45	68	90	113	135	90	113	135	158	180	203	225	16
30		13	25	50	75	100	125	150	100	125	150	175	200	225	250	14
40		14	28	55	83	110	138	165	110	138	165	193	220	248	275	13
50		15	30	60	90	120	150	180	120	150	180	210	240	270	300	12
60		16	33	65	98	130	163	195	130	163	195	228	260	293	325	11
70		18	35	70	105	140	175	210	140	175	210	245	280	315	350	10
80		19	38	75	113	150	188	225	150	188	225	263	300	338	375	9
90		20	40	80	120	160	200	240	160	200	240	280	320	360	400	8
100		21	43	85	128	170	213	255	170	213	255	298	340	383	425	7

a) Twice daily dosing is recommended for pediatric patients under 10 years of age. Once daily dosing is recommended for pediatric patients above 10 years of age and adults.

b) Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 – Age)/Scr. For women, this result should be multiplied by 0.85.

Note: This equation cannot be used for estimating creatinine clearance in infants or pediatric patients. *For pediatric patients*, the modified Schwartz equation may be used as listed below. The formula was based on height in cm and Scr in mg/dL where k is a constant. Ccr is corrected to 1.73 m^2 body surface area. During the first year of life, the value of k is 0.33 for pre-term babies and 0.45 for term infants. The k is 0.55 for pediatric patients and adolescent girls and 0.7 for adolescent boys.

GFR (mL/min/1.73 m2) = (k x Height)/Scr

c) The doses are rounded to whole numbers.

Reviewer's Comments:

- *This section is updated to represent the dose rounded to the nearest whole number in contrast to rounding to the nearest 62.5 mg in the old label. Rounding to the nearest 62.5 mcg is reasonable for the tablet dosage form. With the Oral Solution a finer rounding can be achieved.*
- *This section also expands the body weight range from 50 – 100 kgs (in old label) to 5 – 100 kgs so as to provide the usual maintenance dose for pediatric patients in the table which was not previously provided. Also the table is expanded to provide usual maintenance dose for a twice daily option. For this purpose the peak body stores used in the calculation are* ***10 mcg/kg for age greater than 10 years old*** *and* ***20 mcg/kg for age less than 10 years old****.*
- *The previous label does not provide directions with regard to estimation of creatinine clearance in pediatric patients. Hence, this section is also updated with the modified Schwartz equation for potentially estimating the creatinine clearance in pediatric patients. It should be noted that there are various equations for estimating the creatinine clearance in pediatrics.*

Determination of the target dose in milliliters of Digoxin Oral Solution based on body weight is shown in Table 4. Provided is the volume required per dose, NOT per day.

Table 4: Dose in Milliliters

		Volume to be given in mL:												
Target Dose in mcg/kg →		**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**30**
Weight in kg ↓	**2**	0.08[b]	0.12[b]	0.16[b]	0.2	0.2	0.3	0.4	0.5	0.6	0.6	0.7	0.8	1.2
	3	0.12[b]	0.18[b]	0.2	0.3	0.4	0.5	0.6	0.7	0.8	1.0	1.1	1.2	1.8
	4	0.16[b]	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6	2.4
	5	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	3.0
	6	0.2	0.4	0.5	0.6	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4	3.6
	7	0.3	0.4	0.6	0.7	0.8	1.1	1.4	1.7	2.0	2.2	2.5	2.8	4.2
	8	0.3	0.5	0.6	0.8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2	4.8
	9	0.4	0.5	0.7	0.9	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6	5.4
	10	0.4	0.6	0.8	1.0	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	6.0
	11	0.4	0.7	0.9	1.1	1.3	1.8	2.2	2.6	3.1	3.5	4.0	4.4	6.6
	12	0.5	0.7	1.0	1.2	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8	7.2
	13	0.5	0.8	1.0	1.3	1.6	2.1	2.6	3.1	3.6	4.2	4.7	5.2	7.8
	14	0.6	0.8	1.1	1.4	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6	8.4
	15	0.6	0.9	1.2	1.5	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0	9.0
	20	0.8	1.2	1.6	2.0	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0	12.0
	30	1.2	1.8	2.4	3.0	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0	18.0
	40	1.6	2.4	3.2	4.0	4.8	6.4	8.0	9.6	11.2	12.8	14.4	16.0	24.0
	50	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	14.0	16.0	18	20.0	30.0
	60	2.4	3.6	4.8	6.0	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0	36.0
	70	2.8	4.2	5.6	7.0	8.4	11.2	14.0	16.8	19.6	22.4	25.2	28.0	42.0
	80	3.2	4.8	6.4	8.0	9.6	12.8	16.0	19.2	22.4	25.6	28.8	32.0	48.0
	90	3.6	5.4	7.2	9.0	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0	54.0
	100	4.0	6.0	8.0	10.0	12.0	16.0	20.0	24.0	28.0	32.0	36.0	40.0	60.0

[a] Recommended dosing regimen for pediatric patients under 10 years of age is twice daily. Recommended dosing regimen for pediatric patients over 10 years of age and adults is once daily.

[b] Use calibrated dropper for measurement. In the case of required volume less than 0.2 mL, a separate device such as a graduated syringe is recommended for adequate measurement.

[c] The volumes are rounded to one decimal when greater than 0.2 mL.

Reviewer's Comments:

Table 4 is updated to reflect the changes proposed in Table 3. It should be noted for the pediatric patients (eg: full term babies) weighing less than 4 kg and requiring a maintenance dose less than or equal to 4 mcg/kg, per dose, the calibrated dropper provided with the product will not be able to accurately measure the volume. Hence, the use of a graduated syringe is recommended for such dose.

7.1 P-Glycoprotein (PGP) Inducers/Inhibitors

Digoxin is a substrate for P-glycoprotein, at the level of intestinal absorption, renal tubular section and biliary-intestinal secretion. Therefore, drugs that induce/inhibit P-glycoprotein ~~in intestine or kidney~~ have the potential to alter digoxin pharmacokinetics

Reviewer's Comments:

Above is the Sponsor's proposed change. No additional edits were provided by OCP. As the knowledge of P-gp has been greatly established and improved in the recent years, it is now well known that P-gp locates at intestinal, renal tubular, biliary and brain capillary and plays an important role on the absorption, distribution, metabolism and elimination of drugs which are P-gp substrates. The sponsor proposal in this section is acceptable.

7.2 Pharmacokinetic Drug Interactions on Serum Digoxin Levels in Adults

	Digoxin Serum Concentrations	Digoxin AUC	**Recommendations**
Digoxin exposure increased > 50%			
Amiodarone	70%	NA	Measuring serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 30 % to 50 % and continue monitoring.
Captopril	58%	39%	
Nitrendipine	57%	15%	
Propafenone	35-85%	NA	
Quinidine	100%	NA	
Ranolazine	87%	88%	
Ritonavir	NA	86%	
Verapamil	50-75%	NA	
Digoxin exposure increased < 50%			
Carvedilol	16%	14%	Measuring serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 15 % to 30 % and continue monitoring.
Diltiazem	20%	NA	
Nifedipine	45%	NA	
Rabeprazole	29%	19%	
Telmisartan	20%	NA	
Other literature reported digoxin exposure increase when coadministered with the following drugs, however the magnitude of changes are unclear			
Alprazolam, Azithromycin, Clarithromycin, Cyclosporine, Diclofenac, Diphenoxylate, Epoprostenol, Erythromycin, Esomeprazole, Indomethacin, Itraconazole, Ketoconazole, Lansoprazole, Metformin, Omeprazole, Propantheline, Spironolactone, Tetracycline			Measuring serum digoxin concentrations before initiating concomitant drugs. Continue monitoring and reduce digoxin dose as necessary.

Digoxin exposure decreased	
Acarbose, Activated Charcoal, Albuterol, Antacids, Anti-cancer drugs, Cholestyramine, Colestipol, Exenatide, Kaolin-pectin, Meals High in Bran, Metoclpramide, Miglitol, Neomycin, Rifampin, Salbutamol, St. John's Wort, Sucralfate, Sulfasalazine	Measuring serum digoxin concentrations before initiating concomitant drugs Continue monitoring and increase digoxin dose by approximately 20 % to 40 % as necessary.
No significant Digoxin exposure changes	
Please refer to section 12 for a complete list of drugs which were studies but reported no significant changes on digoxin exposure.	No additional actions are required.

NA – Not available/reported

Reviewer's Comment:
The reporting of the drug interactions for digoxin is made concise by the use of a table. Clarity for this information is provided in the form of classifying drugs based on the magnitude of the pharmacokinetic interaction and the required digoxin dose adjustment is proposed (see Appendix for details).

7.4 Drug-Laboratory Test Interaction

Endogenous substances of unknown composition (digoxin-like immunoreactive substances, DLIS) can interfere with standard radioimmunoassays for digoxin. The interference most often causes results to be falsely positive or falsely elevated, but sometimes it causes results to be falsely reduced. Some assays are more subject to these failings than others. ~~An~~ Several LC/MS/MS methods are ~~is~~ available that may provide ~~a more accurate determination of plasma digoxin levels, however, clinical trials have not been conducted to determine its~~ less susceptibility to DLIS interference. DLIS are present in up to half of all neonates and in varying percentages of pregnant women, patients with hypertrophic cardiomyopathy, patients with renal or hepatic dysfunction, and other patients who are volume-expanded for any reason. The measured levels of DLIS (as digoxin equivalents) are usually low (0.2 to 0.4 ng/mL), but sometimes they reach levels that would be considered therapeutic or even toxic.

In some assays spironolactone, canrenone and potassium canrenoate may be falsely detected as digoxin, at levels up to 0.5 ng/mL. Some traditional Chinese and Ayurvedic medicine substances like Chan Su, Siberian Ginseng, Asian Ginseng, Ashwagandha or Dashen, can cause similar interference.

Spironolactone and DLIS are much more extensively protein-bound than digoxin. As a result, assays of free digoxin levels in protein-free ultrafiltrate (which tend to be about 25% less than total levels, consistent with the usual extent of protein binding) are ~~not~~ less

affected by spironolactone or DLIS. (b) (4) [redacted]

Reviewer's Comment:
The first two paragraphs proposed by the sponsor are acceptable. For the third paragraph, the sponsor's proposed statement appears to be true. However, descriptive data in the labeling would not provide additional benefit, hence; a revision for the third paragraph is provided.

12.3 Pharmacokinetics

Drug-drug Interactions

Based on literature reports no significant changes in digoxin exposure were reported when digoxin was co-administered with the following drugs:

alfuzosin, aliskiren, amlodipine, aprepitant, argatroban, aspirin, atorvastatin, benazepril, bisoprolol, black cohosh, bosentan, candesartan, citalopram, clopidogrel, colesevelam, dipyridamole, disopyramide, donepezil, doxazosin, dutasteride, echinacea, enalapril, eprosartan, ertapenem, escitalopram, esmolol, ezetimibe, famciclovir, felodipine, finasteride, flecainide, fluvastatin, fondaparinux, galantamine, gemifloxacin, grapefruit juice, irbesartan, isradipine, ketorlac, levetiracetam, levofloxacin, lisinopril, losartan, lovastatin, meloxicam, mexilitine, midazolam, milk thistle, moexipril, montelukast, moxifloxacin, mycophenolate, nateglinide, nesiritide, nicardipine, nisoldipine, olmesartan, orlistat, pantoprazole, paroxetine,perindopril, pioglitazone, pravastatin, prazosin, procainamide, quinapril, raloxifene, ramipril, repaglinide, rivastigmine, rofecoxib, ropinirole, rosiglitazone, rosuvastatin, sertraline, sevelamer, simvastatin, sirolimus, solifenacin, tamsulosin, tegaserod, terbinafine, tiagabine, ticlopidine, tigecycline, topiramate, torsemide, tramadol, trandolapril, triamterene, trospium, trovafloxacin, valacyclovir, valsartan, varenicline, voriconazole, zaleplon, zolpidem

Reviewer's comment:

All the reports of no PK interaction have been moved to section 12.3 to be consistent with PLR format.

4 APPENDIX – DETAILED SUMMARY OF SPECIFIC LABELING RECOMMENDATIONS AND INDIVIDUAL LITERATURE REVIEWS

For Section 2.3 Loading dose

Previous label for digoxin elixir did not provide instructions with regard to loading dose. In the current review we proposed to provide this information based on the Loading doses provided in the Lanoxin Injection Pediatrics label. The doses were calculated by multiplying a factor of 1.25 from IV digitalizing doses based on the approximately 80 % absolute bioavailability of Elixir. The table below shows the original calculated values for the doses. Rounded numbers are provided in the label.

Age	Daily Oral Loading Dose, mcg/kg/day
Premature	18.75 - 31.25
Full-Term	25 - 37.5
1 to 24 months	37.5 - 62.5
2 to 5 years	31.25 - 43.75
5 to 10 years	18.75 - 37.5
Over 10 years	10 - 15

For Section 2.4 Estimate of Daily Maintenance Dose

Previous label provided maintenance doses for age greater than 2 years. In the current review we have expanded this to include maintenance dose instructions below 2 years of age. This information was derived from the dosing instructions currently provided in the Lanoxin Injection Pediatrics label.
(http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009330s025lbl.pdf)
The maintenance oral dose was calculated by a factor of 0.25 (range 0.2 – 0.3) of the oral loading dose for premature and 0.3 (range 0.25 – 0.35) for full-term to age less than 10 years old. The table below shows the original calculated values for the doses. Since twice daily regimen is also preferred in pediatric patients less than 10 year age, the Daily maintenance dose is provided for this regimen. Rounded numbers are provided in the label.

Age	Oral Maintenance Dose[a], mcg/kg/day	Oral Maintenance Dose for Twice or Once Daily Dose Regimen, mcg/kg/dose
Premature[b]	4.69 – 7.81	2.34 – 3.91 Twice daily
Full-Term[c]	7.5 – 11.25	3.75 – 5.63 Twice daily
1 to 24 months[c]	11.25 – 18.75	5.63 – 9.38 Twice daily
2 to 5 years[c]	9.38 – 13.13	4.69 – 6.56 Twice daily
5 to 10 years[c]	5.63 – 11.25	2.81 – 5.63 Twice daily
10 to 18 years[c]	3 – 4.5	3 – 4.5 Once daily

The OCP recommended loading and maintenance doses have been compared with two other sources, Harriet Lane and British National Formulary (BNF)*, regarding practice digoxin dosing. Please see tables below for direct comparison of doses for different ages. For age of 10 to 18 years old in BNF, the unit provided in the book is mg/day for loading dose and mcg/day for maintenance dose which is different from the unit used for all other doses. The mg/day and mcg/day unit are converted to mcg/kg/day and shown as the dose (mcg/kg/day) for a 40 kg or 60 kg person. Based on the comparison, the OCP recommended doses fall well in line with the practice dosing.

Loading dose

Oral Solution Label **Age**	**Daily Oral Loading Dose, mcg/kg/day**	Harriret Lane		BNF	
Premature	**20 - 30**	Premature	20	Neonate <1.5kg	25
				Neonate 1.5-2.5kg	30
Full-Term	**25 - 35**	Full-Term	30	Neonate >2.5kg	45
1 to 24 months	**35 - 60**	< 2yr	40-50	1 month-2yr	45
2 to 5 years	**30 - 45**	2 to 10 years	30-40	2 to 5 years	35
5 to 10 years	**20 - 35**			5 to 10 years	25
Over 10 years	**10 - 15**	>10 yr and <100kg	10-15	10-18 yr	**0.75-1.5 mg/day**
1/2 TDD for the first dose, then Additional fractions of this planned total dose may be given at 4- to 8-hour intervals		1/2 TDD, then 1/4 TDD Q8-18h x 2 Doses; ECG 6h after dose for toxicity		3 divided dose for first 24h	

unit: mcg/kg/day

	0.75mg/day	1.5mg/day
40kg	18.75	37.5
60kg	12.5	25

*: Harriet Lane, page 804-805, 2009 edition; BNF, page 96-99, 2009 edition

Maintenance dose

Oral Solution Label **Age**	**Oral Maintenance Dose, mcg/kg/day**	Harriret Lane		BNF	
Premature	**4.7 – 7.8**	Premature	5	Neonate <1.5kg	4 - 6
				Neonate 1.5-2.5kg	4 - 6
Full-Term	**7.5 – 11.3**	Full-Term	8 - 10	Neonate >2.5kg	10
1 to 24 months	**11.3 – 18.8**	< 2yr	10 - 12	1 month-2yr	10
2 to 5 years	**9.4 – 13.1**	2 to 10 years	8 - 10	2 to 5 years	10
5 to 10 years	**5.6 – 11.3**			5 to 10 years	6
Over 10 years	**3.0 – 4.5**	>10 yr and <100kg	2.5 - 5	10-18 yr	**62.5-250 mcg/day**
<10yr: BID >=10yr: QD		<10yr: BID >=10yr: QD		1-2 divided dose after 24h	

unit: mcg/kg/day

	62.5mcg/day	250mcg/day
40kg	1.56	6.25
60kg	1.04	4.17

For Section 2.5 Adjustment of Dose:

Dosing regimen for renal impaired patients was provided only for adults in the original label. There is apparently a need for recommendations of dose adjustment for renal impaired children which is now included.
Based on previous review in 2004 by Dr. Venkatesh Atul Bhattaram and the current Lanoxin Tablet Label*: The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:*
Maintenance Dose = Peak Body Stores (i.e., Loading Dose) × % Daily Loss/100
Where: % Daily Loss = 14 + Ccr/5

The old label appeared to use the formula (for IV formulation) and multiply by a factor of 1.25 (for elixir) and then use the increment of 62.6 mcg for doses lower than 250 mcg and increment of 125 mcg for doses higher than 250 mcg. This approach is reasonable for tablets as they are available as 125 mg scored tablets but inappropriate for the elixir formulation. However, for the Oral Solution a more accurate rounding is feasible which is reflected in the current label.

The maintenance dose calculation for adults is based on a loading dose of 10 mcg/kg. The loading dose in pediatrics below 10 years age is 2 – 4 fold higher. For the calculation of the maintenance dose in children a more conservative approach of using 20 mcg/kg was taken as the loading dose table.

Further, as indicated in the old footnote, the equation (CG) used for renal function estimation is for adults only and cannot be used for children. Based on two draft guidance: **General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological** and **Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling Products**, here provided the modified Schwartz equation to estimate renal function for children. The formula (see below) was based on height in cm and serum creatinine clearance (Ccr) in mg/dL where Ccr is corrected to 1.73 m^2 body surface area. During the first year of life, the value of k is 0.33 for pre-term babies and 0.45 for term infants. The k is 0.55 for pediatric patients and adolescent girls and 0.7 for adolescent boys.
GFR (mL/min/1.73 m2) = (k x Height)/Scr

In the old label, the volume for the drug to be dispensed was provided up to dose of 10 mcg/kg and the weight range was provided from 10 kg to 100 kg. As shown in the section 2.3 Loading dose, the largest daily dose is 60 mcg/kg with roughly half the total given as the first dose which gives 30 mcg/kg. The table now includes doses greater than 10 mcg/kg and up to 30 mcg/kg to accommodate the need. In addition, as body weight of 10 kg did not cover the younger children, weight range now includes 2 kg to 10 kg where the average weights for full-term babies are around 3.5 kg based on CDC Growth Chart 2005.

In addition, as the smallest measurable volume of the attached calibrated dropper is 0.2 mL, and marked in divisions of 0.1 mL, the calculated values are rounded to one decimal when it is greater than 0.2 mL in the final label.

It should be noted for the pediatric patients (eg: full term babies) weighing less than 4 kg and requiring a maintenance dose less than or equal to 4 mcg/kg, per dose, the calibrated dropper provided with the product will not be able to accurately measure the volume. Hence, the use of a graduated syringe is recommended for such doses.

Table below is the original values with demonstration of the body weight distribution for different age groups of full-term babies, 6-month old, 12-month old, 24-month old and 10 years old.

Dose in Milliliters

		Target Dose in mcg/kg:												
		2	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**30**
[b]	**2**	0.08	0.12	0.16	0.2	0.24	0.32	0.4	0.48	0.56	0.64	0.72	0.8	1.2
	3	0.12	0.18	0.24	0.3	0.36	0.48	0.6	0.72	0.84	0.96	1.08	1.2	1.8
	4	0.16	0.24	0.32	0.4	0.48	0.64	0.8	0.96	1.12	1.28	1.44	1.6	2.4
	5	0.2	0.3	0.4	0.5	0.6	0.8	1	1.2	1.4	1.6	1.8	2	3
	6	0.24	0.36	0.48	0.6	0.72	0.96	1.2	1.44	1.68	1.92	2.16	2.4	3.6
Weight in kg	**7**	0.28	0.42	0.56	0.7	0.84	1.12	1.4	1.68	1.96	2.24	2.52	2.8	4.2
	8	0.32	0.48	0.64	0.8	0.96	1.28	1.6	1.92	2.24	2.56	2.88	3.2	4.8
	9	0.36	0.54	0.72	0.9	1.08	1.44	1.8	2.16	2.52	2.88	3.24	3.6	5.4
	10	0.4	0.6	0.8	1	1.2	1.6	2	2.4	2.8	3.2	3.6	4	6
	11	0.44	0.66	0.88	1.1	1.32	1.76	2.2	2.64	3.08	3.52	3.96	4.4	6.6
	12	0.48	0.72	0.96	1.2	1.44	1.92	2.4	2.88	3.36	3.84	4.32	4.8	7.2
	13	0.52	0.78	1.04	1.3	1.56	2.08	2.6	3.12	3.64	4.16	4.68	5.2	7.8
	14	0.56	0.84	1.12	1.4	1.68	2.24	2.8	3.36	3.92	4.48	5.04	5.6	8.4
	15	0.6	0.9	1.2	1.5	1.8	2.4	3	3.6	4.2	4.8	5.4	6	9
	20	0.8	1.2	1.6	2	2.4	3.2	4	4.8	5.6	6.4	7.2	8	12
	30	1.2	1.8	2.4	3	3.6	4.8	6	7.2	8.4	9.6	10.8	12	18
	40	1.6	2.4	3.2	4	4.8	6.4	8	9.6	11.2	12.8	14.4	16	24
	50	2	3	4	5	6	8	10	12	14	16	18	20	30
	60	2.4	3.6	4.8	6	7.2	9.6	12	14.4	16.8	19.2	21.6	24	36
	70	2.8	4.2	5.6	7	8.4	11.2	14	16.8	19.6	22.4	25.2	28	42
	80	3.2	4.8	6.4	8	9.6	12.8	16	19.2	22.4	25.6	28.8	32	48
	90	3.6	5.4	7.2	9	10.8	14.4	18	21.6	25.2	28.8	32.4	36	54
	100	4	6	8	10	12	16	20	24	28	32	36	40	60

[a] Recommended dosing regimen for children under 10 years of age is twice daily. Recommended dosing regimen for children over 10 years of age and adults is once daily.

[b] Red line: Weight range for full-term babies including boys and girls. Range shown is from 5% to 95 % percentile (2.6-4.4 kg)

Purple line: Weight range for 6-month old infants including boys and girls. Range shown is from 5% to 95 % percentile (6-9.6 kg)
Orange line: Weight range for 12-month old toddlers including boys and girls. Range shown is from 5% to 95 % percentile (8-12.4 kg)
Blue line: Weight range for 24-month old toddlers including boys and girls. Range shown is from 5% to 95 % percentile (10.2-15.4 kg)
Green line: Weight range for 10-year old children including boys and girls. Range shown is from 5% to 95 % percentile (25-46 kg)

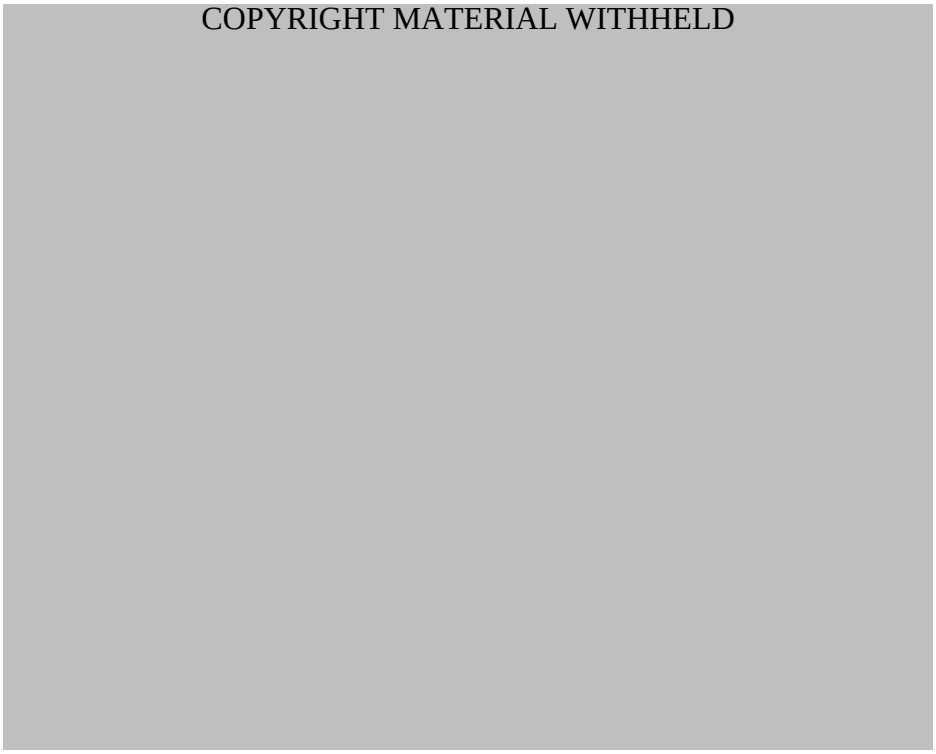
For Section 7.1 P-Glycoprotein (PGP) Inducers/Inhibitors

Review

P-glycoprotein related drug interactions: clinical importance and a consideration of disease states

Caroline A Lee†, Jack A Cook, Eric L Reyner & Dennis A Smith

Expert Opin Drug Metab Toxicol. 2010 May; 6(5): 603-19



OCP Recommendations: No actions are required. The sponsor's proposal "*Digoxin is a substrate for P-glycoprotein, at the level of intestinal absorption, renal tubular section and biliary-intestinal secretion. Therefore, drugs that induce/inhibit P-glycoprotein ~~in intestine or kidney~~ have the potential to alter digoxin pharmacokinetics*" is acceptable.

Source: Expert Opin Drug Metab Toxicol. 2010 May; 6(5): 603-19 (http://informahealthcare.com/doi/pdf/10.1517/17425251003610640)

For Section 7.2 Pharmacokinetic Drug Interactions

Although the sponsor's proposal to include new drug-drug interaction information is acceptable, a different approach for this section was taken by OCP to exclude all descriptions with inconsistent instructions for the potential drug-drug interactions and divide all information in this section into 5 categories: (1) digoxin exposure to increase greater than 50 %, (2) less than 50 %, (3) reported to increase without available data, (4) digoxin exposure to decrease and (5) no significant changes due to the interactions where the list of drugs for non-significant interactions be moved to Section 12.3 Pharmacokinetics, Drug-Drug Interaction.

As noted in the table in Section 7.2 of the proposed label, measuring serum digoxin concentrations is recommended before initiating interacting drugs. For the category of greater than 50% increase, digoxin dose reduction by approximately 30 % to 50 % and continue monitoring is recommended. The approach is to try to maintain the digoxin levels when initiating an interacting drug. While the reported data shows the exposure increase of digoxin could be as high as 100 %, the calculation was done at scenarios of 50

% and 100 % increase. For example, with the digoxin level at 1 ng/mL before a concomitant drug which is expected to increase digoxin level by 50 %, a 30 % reduction of digoxin dose (bring the exposure down to 0.7 ng/mL) and a subsequent increase in 50 % will bring the digoxin level back to ~1 ng/mL. Similarly, for a concomitant drug which increases digoxin level by 100 %, a 50 % reduction of digoxin dose (bring the exposure down to 0.5 ng/mL) and a subsequent increase in 100 % will bring the digoxin level back to 1 ng/mL.

For the category of less than 50 % increase in digoxin levels, digoxin dose reduction by approximately 15 % to 30 % and continue monitoring is recommended. Same approach as described above was applied. Scenarios of concomitant drugs which increase digoxin level by 20 % and 50 % were calculated which provide the values of 15 % and 30 % reduction for digoxin dose, respectively.

For the category of reported increase without available data, continue monitoring and reduce digoxin dose as necessary is recommended as the magnitude of exposure changes are not known.

Same approach has been taken for the scenario of potential digoxin exposure decrease. As the magnitude of change is not known for most drugs under this category, 20 % to 30 % decrease of digoxin exposure was reported by miglitol and exenatide coadministration. Based on this data, the recommendation is to continue monitoring and increase digoxin dose by approximately 20 % to 40 % as necessary.

Anti-anginal Drugs: Ranolazine

The supportive evidence for this drug-drug interaction was obtained from FDA Summary Basis of Approval, NDA 021-526 (Ranexa® Tablets). A summary of this review is provided below.

STUDY CVT 3021 - A DOUBLE-BLIND, RANDOMIZED, PARALLEL, PHARMACOKINETIC AND SAFETY STUDY OF RANOLAZINE SR 750 MG TWICE A DAY ADMINISTERED ALONE AND IN COMBINATION WITH DIGOXIN 0.125 MG ONCE A DAY IN PATIENTS WITH CONGESTIVE HEART FAILURE

STUDY INVESTIGATOR AND SITE: Multiple Investigators and sites

Report No: CVT 3021
Volume No: 53-63, ITEM 6

(FDA Summary Basis of Approval, NDA 021-526 (Ranexa® Tablets))

STUDY DESIGN

This was a multi-center, double-blind, randomized placebo controlled, parallel group PK and safety study of ranolazine SR 750 mg administered with digoxin 0.125 mg or digoxin placebo in male and female patients in the age between 18 and 75 years with NYHA Class III and IV CHF with right ventricular ejection fraction (RVEF) <35%. The study comprised a 2 week screening period (Days -14 to Day-1), a double-blind digoxin/digoxin placebo run-in phase (Days 1-8), a double-blind ranolazine/ranolazine placebo treatment phase (Days 9-14) with study termination on Day 16. Based on the results of study CVT 3011 a sample size of 13 per treatment was determined to be sufficient to demonstrate the absence of an interaction with 80% power for digoxin AUC0-24 and Cmax.

The dosing schedule is outlined in the following table:

Dosing Regimen

Treatment Group	Double-Blind Digoxin Run-In Phase Days 1-8	Double-Blind Inpatient Treatment Phase Days 9-14			
	Time of Dose (hours)				
	0	0	2	12	14*
	Dose 1 (eg, 8 AM)	Dose 1 (eg, 8 AM)	Dose 2 (eg, 10 AM)	Dose 3 (eg, 8 PM)	Dose 4 (eg, 10 PM)
A	DP	RP, DP	RP	RP	RP
B	DP	RA, DP	RP	RA	RP
C	DA	RP, DA	RP	RP	RP
D	DA	RA, DA	RP	RA	RP
E	DA	RP, DA	RA	RP	RA

Where:
RA = Ranolazine Active
RP = Ranolazine Placebo
DA = Digoxin Active
DP = Digoxin Placebo

* On Day 14 only the morning ranolazine dose was administered.

PK RESULTS

Table J. Digoxin Pharmacokinetic Parameters at Steady State (Day 14)

Parameter	Treatment: Digoxin 0.125 mg QD + Ranolazine placebo BID (Group C (n=18))	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID (Group D (n=16))	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID 2 hours post digoxin dose (Group E (n=16))
AUC_{0-24} (hr.ng/mL) Mean (SD) Range	11.5485 (4.37782) [	21.7601 (12.26450)	16.2178 (7.04606)]
C_{max} (ng/mL) Mean (SD) Range	0.9502 (0.25787) [	1.5975 (0.76309)	1.2401 (0.57682)]
T_{max} (hr) Mean (SD) Range	1.192 (0.7499) [	1.516 (0.9358)	1.668 (1.0018)]
C_{ave} (ng/mL) Mean (SD) Range	0.4812 (0.18241) [	0.9067 (0.51102)	0.6757 (0.29359)]
C_{min} (ng/mL) Mean (SD) Range	0.2886 (0.11501) [	0.5432 (0.34469)	0.3619 (0.18129)]
λ_z (1/hr) Mean (SD) Range	0.0309 (0.03341) [	0.0224 (0.01311)	0.0304 (0.02026)]
$t_{1/2}$ (hr) Mean (SD) Range	31.994 (13.0023) [	43.147 (27.3118)	27.859 (10.0255)]

Digoxin pharmacokinetic changes with or without co-administration of ranolazine are recalculated by the reviewer and provided in the table below:

Digoxin Pharmacokinetics

	Group C	Group D	Ratio(D/C)
AUC0-24	11.55	21.76	**1.88**
Cmax	0.95	1.60	**1.68**
Cave	0.48	0.91	**1.88**
Cmin	0.29	0.54	**1.87**

OCP Recommendations: The sponsor's statement "*Concomitant administration of ranolazine 750 mg twice daily with digoxin 0.125 mg daily increased steady-state AUC(0-24) and Cmax by 88.4% and 68.1%, respectively in patients with NYHA class III and IV congestive heart failure via P-GP inhibition.*" appears to be true. Ranolazine will be placed under the category of greater than 50% increase of digoxin exposure.

Source: FDA Summary Basis of Approval, NDA 021-526 (Ranexa® Tablets).

Renin Inhibitor: Aliskiren

Pharmacokinetics of the Oral Direct Renin Inhibitor Aliskiren in Combination With Digoxin, Atorvastatin, and Ketoconazole in Healthy Subjects: The Role of P-Glycoprotein in the Disposition of Aliskiren

Sujata Vaidyanathan, PhD, Gian Camenisch, PhD, Helmut Schuetz, PhD, Christine Reynolds, Ching-Ming Yeh, PhD, Marie-Noelle Bizot, PhD, Hans Armin Dieterich, MD, Dan Howard, PhD, and William P. Dole, MD

J Clin Pharm 2008; 48: 1323-38.

CNS Drugs: Midazolam

Simultaneous Measurement of In Vivo P-glycoprotein and Cytochrome P450 3A Activities

Brian Kirby, Evan D. Kharasch, MD, PhD, Kenneth T. Thummel, PhD, Vishal S. Narang, PhD, Christine J. Hoffer, CCRC, and Jashvant D. Unadkat, PhD

J Clin Pharmacol. 2006 Nov; 46(11):1313-9

Antibacterial Drugs: Tigecycline

Absence of an Interaction Between Tigecycline and Digoxin in Healthy Men

James J. Zimmerman, Ph.D., Dawn M. Harper, B.A., Kyle Matschke, M.S., John L. Speth, Ph.D., Donald G. Raible, M.D., and Richard J. Fruncillo, M.D., Ph.D.

Pharmacotherapy. 2007 Jun; 27(6):835-44

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OCP Recommendations: No actions are required. The sponsor proposed "(b) (4) " is acceptable

Source: Pharmacotherapy. 2007 Jun; 27(6):835-44
(http://www.ncbi.nlm.nih.gov/pubmed/17542766)

Antiviral Drugs: Ritonavir

Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers

Reinhard Ding, MD, Yorki Tayrouz, MD, Klaus-Dieter Riedel, BSc, Jürgen Burhenne, PhD, Johanna Weiss, PhD, Gerd Mikus, MD, and Walter E. Haefeli, MD *Heidelberg, Germany*

Clin Pharm Ther 2004; 76(1): 73-84

Digoxin pharmacokinetic changes with or without co-administration of ritonavir are reanalyzed by the reviewer and provided in the table below:

Digoxin Pharmacokinetics

	Digoxin+Placebo (D)	Digoxin+Ritonavir(D+R)	Ratio(D+R/D)
AUC0-∞	22.00	41.00	**1.86**
Clnr 0-∞	215.00	112.00	**0.52**
Clr 0-∞	194.00	126.00	**0.65**

OCP Recommendations: The sponsor's statement "*Concomitant administration of intravenous digoxin and ritonavir in healthy male volunteers resulted in an 86% increase in digoxin AUC and decreased nonrenal and renal digoxin clearance by 48% and 35%, respectively. Serum digoxin concentrations should be monitored when these drugs are administered together and dosage adjustments may be warranted.*" appears to be true. Ritonavir will be placed under category of greater than 50% increase of digoxin exposure.

Source: Clin Pharm Ther 2004; 76(1): 73-84 (http://www.nature.com/clpt/journal/v76/n1/pdf/clpt2004462a.pdf)

Glucose Lowering Drugs: Exenatide

Effect of Exenatide on the Steady-State Pharmacokinetics of Digoxin

Prajakti A. Kothare, PhD, Danny K. W. Soon, MBBS, Helle Linnebjerg, MSc, PhD, Soomin Park, PhD, Clark Chan, Adeline Yeo, MSc, Maggie Lim, Kenneth F. Mace, PhD, and Stephen D. Wise, FRCP, FFPM

J Clin Pharmacol. 2005 Sep; 45(9): 1032-7

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OCP Recommendations: The sponsor's statement for 17% decrease of Cmax is true. The statement for delaying gastric emptying is not appropriate. Although co-administration of exenatide increased Tmax from 1.5 hours to 4.0 hours which might be of clinical significance, no evidence was shown to suggest that the increase of Tmax was due to the particular mechanism of delaying gastric emptying. Exenatide will be placed under the category of decreased digoxin exposure.

Source: J Clin Pharmacol. 2005 Sep; 45(9): 1032-7
(http://www.jclinpharm.org/cgi/content/abstract/45/9/1032)

Anti-cholinergic Drugs: Trospium

Predictive Power of an In Vitro System to Assess Drug Interactions of an Antimuscarinic Medication: A Comparison of In Vitro and In Vivo Drug-Drug Interaction Studies of Trospium Chloride With Digoxin

B. Sandage, PhD, L. Sabounjian, RN, J. Shipley, MD, A. Profy, PhD, K. Lasseter, MD, L. Fox, and M. Harnett, MS

J Clin Pharmacol 2006 Jul; 46(7):776-84

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Digoxin pharmacokinetic changes with or without co-administration of trospium are reanalyzed by the reviewer and provided in the table below:

Digoxin Pharmacokinetics

	Digoxin+Trospium(D+T)	Digoxin(D)	Ratio(D+T/D)
AUC0-∞	32478.00	30595.00	**1.06**
Cmax	2478.00	2309.00	**1.07**

OCP Recommendations: No actions are required. The sponsor proposed (b) (4) is acceptable.

Source: J Clin Pharmacol 2006 Jul;46(7):776-84
(http://jcp.sagepub.com/content/46/7/776.long)

Anti-cholinergic Drugs: Solifenacin

Multiple doses of the antimuscarinic agent solifenacin do not affect the pharmacodynamics or pharmacokinetics of warfarin or the steady-state pharmacokinetics of digoxin in healthy subjects

R. A. Smulders, M. E. Kuipers & W. J. J. Krauwinkel
Astellas Pharma Europe B.V., Leiderdorp, the Netherlands

Br J Clin Pharmacol. 2006 Aug; 62(2):210-7

Digoxin pharmacokinetic changes with or without co-administration of solifenacin are reanalyzed by the reviewer and provided in the table below:

Digoxin Pharmacokinetics

	Digoxin(D)	Digoxin+Solifenacin(D+S)	Ratio(D+S/D)
Cmax	0.93	1.05	**1.13**
AUC,ss	8.43	8.74	**1.04**

OCP Recommendations: No actions are required. The sponsor proposed [redacted] (b) (4) is acceptable.

Source: Br J Clin Pharmacol. 2006 Aug; 62(2):210-7 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1885095/?tool=pubmed)

Herbal Products: Echinacea

Gauging the clinical significance of P-glycoprotein-mediated herb-drug interactions: Comparative effects of St. John's wort, echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics

Bill J. Gurley[1], **Ashley Swain**[2], **D. Keith Williams**[3], **Gary Barone**[4], and **Sunil Kumar Battu**[5]

Mol Nutr Food Res 2008; 52: 772-9

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Digoxin pharmacokinetic changes with or without co-administration of echinacea are reanalyzed by the reviewer and provided in the table below:

Digoxin pharmacokinetics

		AUC	AUC ratio (post/pre)	Cmax	Cmax ratio (post/pre)
pre- post-	Echinacea	7.3 7.5	**1.03**	1.3 1.2	**0.92**

OCP Recommendations: No actions are required. The sponsor proposed (b) (4) is acceptable.

Source: Br Mol Nutr Food Res 2008; 52: 772-9 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562898/?tool=pubmed)

Herbal Products: Milk thistle and Black cohosh

EFFECT OF MILK THISTLE (*SILYBUM MARIANUM*) AND BLACK COHOSH (*CIMICIFUGA RACEMOSA*) SUPPLEMENTATION ON DIGOXIN PHARMACOKINETICS IN HUMANS

Bill J. Gurley, Gary W. Barone, D. Keith Williams, Julie Carrier, Philip Breen, C. Ryan Yates, Peng-fei Song, Martha A. Hubbard, Yudong Tong, and Sreekhar Cheboyina

Drug Metab Dispos. 2006 Jan; 34(1): 69-74

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Digoxin pharmacokinetic changes with or without co-administration of milk thistle or black cohosh are reanalyzed by the reviewer and provided in the table below:

Digoxin pharmacokinetics

		AUC	AUC ratio (post/pre)	Cmax	Cmax ratio (post/pre)
pre-	milk thistle	13.8		3	
post-		12.5	**0.91**	2.6	**0.87**
pre-	black cohosh	13.2		2.8	
post-		13.9	**1.05**	2.9	**1.04**

OCP Recommendations: No actions are required. The sponsor proposed (b) (4) is acceptable.

Source: Drug Metab Dispos. 2006 Jan; 34(1): 69-74 (http://dmd.aspetjournals.org/content/34/1/69.full.pdf)

Antiarrhythmic drugs: Quinidine

The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. A prospective study.

Ann Intern Med. 1980 May;92(5):605-8.

OCP Recommendations: The increase of digoxin exposure has been determined to be 100 % based on this report.

Source: Ann Intern Med. 1980 May;92(5):605-8
(http://www.ncbi.nlm.nih.gov/pubmed/7387000)

For Section 7.4 Drug-Laboratory Test Interaction

Therapeutic Drug Monitoring of Digoxin

Impact of Endogenous and Exogenous Digoxin-Like Immunoreactive Substances

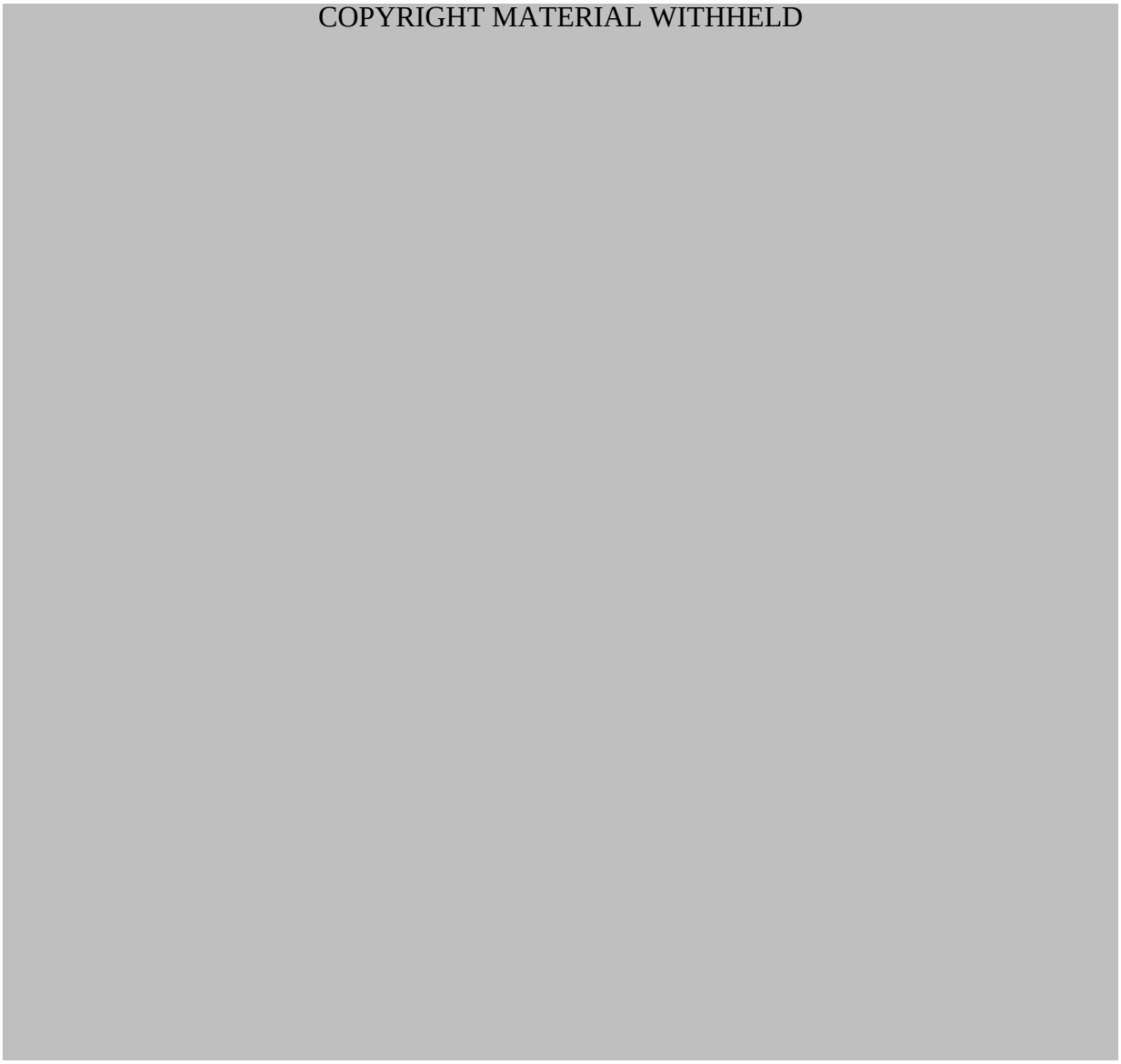
Amitava Dasgupta

Toxicol Rev. 2006; 25(4):273-81.

OCP Recommendations: No actions are required. The sponsor's proposal is acceptable.

2. Sponsor's proposal (blue highlights demonstrate new information): *Some traditional Chinese and Ayurvedic medicine substances like Chan Su, Siberian Ginseng, Asian Ginseng, Ashwagandha or Dashen, can cause similar interference.*

Background: Similarly, Chan Su contains bufadienolides such as bufalin which also has similar structure with digoxin.



OCP Recommendations: No actions are required. The sponsor's proposal is acceptable.

Source: Toxicol Rev. 2006; 25(4):273-81 (http://adisonline.com/toxicology/pages/articleviewer.aspx?year=2006&issue=25040&article=00007&type=abstract)

Measuring the Unbound Concentration Fails to Resolve Analytic Interferences in Digoxin Immunoassays

Raymond G. Morris, PhD,† Terry E. Jones, PhD,‡ Fiona A. Wicks, BSc,* and Natasha M. Rogers, MBBS§*

Ther Drug Monit. 2008 Aug; 30(4):548-52.

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OCP Recommendations: The sponsor's proposed statement appears to be true. However, descriptive data in the labeling would not provide additional benefit. The recommended revision is provided as follows "*It should be noted that ultrafiltration does not solve all interference problems with alternative medicines.* (b) (4) "

Source: Ther Drug Monit. 2008 Aug; 30(4):548-52. (http://www.ncbi.nlm.nih.gov/pubmed/18641559)

Therapeutic monitoring of serum digoxin for patients with heart failure using a rapid LC-MS/MS method

Shuijun Li [a,b], Gangyi Liu [a], Jingying Jia [a], Yi Miao [a], Shuiming Gu [c], Peizhi Miao [c], Xueying Shi [d], Yiping Wang [b], Chen Yu [a,*]

Clin Biochem. 2010 Feb; 43(3):307-13

OCP Recommendations: The sponsor's proposed statement is considered acceptable. A recommended revision is provided as follows" *The use of an LC/MS/MS method* (b) (4) *may be the better option according to the good results it provides, especially in term of specificity and limit of quantization*."

Source: Clin Biochem. 2010 Feb;43(3):307-13 (http://www.ncbi.nlm.nih.gov/pubmed/19833118)

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/s/

Ju Ping LAI
08/24/2011

RAJANIKANTH MADABUSHI
08/24/2011
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021648Orig1s004

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: September 15, 2011

To: Alexis Childers – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 21648 Digoxin Oral Solution, USP

DDMAC has reviewed the proposed product labeling (PI) Digoxin Oral Solution, USP, submitted for consult on September 1, 2011.

The following comments are provided in response to the updated proposed PI sent via email on Septebmer 1, 2011 by Alexis Childers. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EMILY K BAKER
09/15/2011

RHPM Review of Draft Labeling
NDA 21648/S - 004

Date of Submission:	June 11, 2010
Date of Receipt:	June 14, 2010
Date of Review:	September 1, 2011
Applicant Name:	Roxane Laboratories Inc
Product Name:	Digoxin Oral Solution .05 mg/ml

Background: Digoxin elixir, (now known as digoxin oral solution) originally approved in 2004, is a cardiac glycoside that is indicated for the treatment of heart failure and atrial fibrillation. Roxane submitted supplement 4 in response to the Division's June 2010 letter requesting PLR conversion. After submitting the PLR, Roxane provided an amendment in October 2010 incorporating changes from the Lanoxin label as well as published literature.

The entire label has been revised to conform to the PLR format. In addition the following content related changes have been made:

1. The term "children" was changed to pediatric patients throughout the label.

2. In **INDICATIONS AND USAGE,** subsections were created to delineate between adults and pediatric patients.

3. Under **INDICATIONS AND USAGE**, section **1.1 Heart Failure in Adults** the second sentence was changed from:

   Digoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality.

   To read as follows:

   Digoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by increased exercise capacity and decreased heart failure-related hospitalizations and emergency care, while having no effect on mortality.

4. Under **INDICATIONS AND USAGE** section **1.2 Heart Failure in Pediatric Patients** was added and reads as:

   Digoxin increases myocardial contractility in pediatric patients with heart failure.

5. Under **INDICATIONS AND USAGE** section **1.3 Atrial Fibrillation in Adults,** the last sentence was deleted and the following statement was added:

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

6. The entire **DOSAGE AND ADMINISTRATION** section was reorganized, and rewritten. The sections was changed from:

2 DOSAGE AND ADMINISTRATION

Because the pharmacokinetics of digoxin are complex, and because toxic levels of digoxin are only slightly higher than therapeutic levels, digoxin dosing can be difficult. The recommended approach is to

- estimate the patient's daily maintenance dose;
- adjust the estimate to account for patient-specific factors;
- choose a dosing regimen;
- monitor the patient for toxicity and for therapeutic effect, if possible; and
- adjust the dose.

2.1 Estimate of Daily Maintenance Dose

The recommended initial estimates for daily oral doses of digoxin are:

Table 1: Estimate the Daily Maintenance Dose

Age	Daily Oral Dose, mcg/kg/day
Children > 2 years	10
Prepubertal children	10
Adults	3

These doses will, in uncomplicated patients, tend to produce steady-state post-absorptive levels of 1 to 2 ng/mL, but the confidence limits around this range are wide.

2.2 Adjustment of the Estimated Dose

As noted in CLINICAL PHARMACOLOGY (12.3) and in DRUG INTERATCTIONS (7), the body's handling of digoxin can be affected by many different patient-specific factors. Some of the possible effects are usually small, so anticipatory dose adjustment might not be required, but others should be considered before initial dosing. Patients with abnormal renal function need to have their doses of digoxin proportionately reduced. Normal developmental changes in pediatric renal function were factored into the table given in the previous subsection, but age-related (or other) changes in adult renal function were not. The effects of renal function on recommended digoxin doses in adults is shown in Table (b) (4) below. For children with known or suspected renal dysfunction, lower starting doses should be considered combined with frequent monitoring of digoxin levels.
Digoxin's volume of distribution is proportional to lean body weight, and the table in the previous section assumes that patients are of average composition. The dose of digoxin must be reduced in patients whose lean body weight is —

typically because of obesity or edema — an abnormally small fraction of their total body mass.

Concomitant drug use should be considered when adjusting the estimated digoxin dose. [see DRUG INTERACTIONS (b) (4)]

NOTE: The calibrated dropper supplied with the 60 mL bottle of digoxin (b) (4) is not appropriate to measure doses below 0.2 mL. Doses less than 0.2 mL require appropriate methods or measuring devices designed to administer an accurate amount to the patient.

Table (b) (4) provides average daily maintenance dose requirements of digoxin for patients with heart failure based upon lean body weight and renal function.

Table (b) (4): Usual Daily Maintenance Dose Requirements (mcg) of Digoxin for Estimated Peak Body Stores of 10 mcg/kg in Adults

Corrected Ccr (mL/min/70 kg)[a]	Lean Body Weight							Number of Days Before Steady State Achieved
	kg lb	50 110	60 132	70 154	80 176	90 198	100 220	
0		62.5[b]	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

a) Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 – Age)/Scr. For women, this result should be multiplied by 0.85. *Note*: This equation cannot be used for estimating creatinine clearance in infants or children.

b) 62.5 mcg = 0.0625 mg

Table (b) (4): Daily Dose in Milliliters

		Target Dose in mcg/kg/day:						
		2	**3**	**4**	**5**	**6**	**8**	**10**
Weight In kg	**10**	0.4	0.6	0.8	1	1.2	1.6	2
	11	0.44	0.66	0.88	1.1	1.32	1.76	2.2
	12	0.48	0.72	0.96	1.2	1.44	1.92	2.4
	13	0.52	0.78	1.04	1.3	1.56	2.08	2.6
	14	0.56	0.84	1.12	1.4	1.68	2.24	2.8
	15	0.6	0.9	1.2	1.5	1.8	2.4	3
	20	0.8	1.2	1.6	2	2.4	3.2	4
	30	1.2	1.8	2.4	3	3.6	4.8	6
	40	1.6	2.4	3.2	4	4.8	6.4	8
	50	2	3	4	5	6	8	10
	60	2.4	3.6	4.8	6	7.2	9.6	12
	70	2.8	4.2	5.6	7	8.4	11.2	14
	80	3.2	4.8	6.4	8	9.6	12.8	16
	90	3.6	5.4	7.2	9	10.8	14.4	18
	100	4	6	8	10	12	16	20

On the left side of the chart, locate the patient's weight in kilograms. At the top of the chart, identify which dose in mcg/kg/day will be used for this patient. The block on the chart at which the two rows (weight and target dose) intersect is the milliliter amount that should be given to the patient.

2.3 Patient Monitoring

Dosing as described above may need to be increased or decreased, depending upon the patient's response, so patients must be monitored for signs of efficacy and toxicity.

When the purpose of digoxin therapy is reduction of resting ventricular response to atrial tachyarrhythmia, a therapeutic digoxin effect may be obvious. In other settings, however, the therapeutic effect of digoxin may be difficult to separate from other developments in the course of the underlying disease.

Similarly, digoxin toxicity may be easily identified when there are pathognomonic findings of new atrioventricular block, or of yellow/green discoloration of vision. Other manifestations of digoxin toxicity (*e.g.*, nausea) might have alternative explanations, and symptoms of toxicity may be difficult to evaluate in small children and other inarticulate patients. It will therefore often be necessary to monitor digoxin therapy by means of serum digoxin levels.

Because hypokalemia or hypomagnesia can greatly increase the risk of digoxin toxicity, it is appropriate to monitor these levels whenever digoxin levels are measured.

Digoxin should be allowed to distribute into its volume of distribution before measurement, so specimens for these assays should not be collected until 6 to 8 hours after the time of administration. In general, serum levels below 0.5 ng/mL are unlikely to be beneficial, while levels above 2 ng/mL are associated with increased toxicity without increased benefit. Within the 0.5 to 2 ng/mL range, the inotropic effects of digoxin tend to appear at lower concentrations than the electrophysiological effects.
When decision-making is to be guided by serum digoxin levels, the clinician must consider the possibility of reported concentrations that have been falsely elevated by endogenous digoxin-like immunoreactive substances [see (b) (4)]. If the assay being used is sensitive to these substances, it may be prudent to obtain a baseline measurement before digoxin therapy is started, and correct later values by the reported baseline level.

2.4 Dose Adjustment

The monitoring described above may suggest increases or decreases in digoxin doses. Additional monitoring, and in some cases anticipatory dose adjustment, may be indicated around the time of various changes in the patient's internal milieu, including

- normal development through childhood;
- concomitant drug use should be considered when adjusting the estimated digoxin dose [see DRUG INTERACTIONS (b) (4)].
- new co-administration of an antibiotic, especially if the patient had required high doses of digoxin in order to achieve modest serum concentrations, raising the suspicion that a substantial fraction of administered digoxin was being destroyed by colonic bacteria; and
- changes in renal function (see Table (b) (4) above).

To read as follows:

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

The dose of digoxin should be based on clinical assessment but individual patient factors should be taken into consideration. Those factors are:

- Lean body weight
- Renal function
- Patient age
- Concurrent disease *[see Warnings and Precautions (6)]*
- Concomitant medication *[see Drug Interactions (7)]*

Because the pharmacokinetics of digoxin are complex, and because toxic levels of digoxin are only slightly higher than therapeutic levels, digoxin dosing can be difficult. The recommended approach is to

- estimate the patient's daily maintenance dose
- adjust the estimate to account for patient-specific factors
- choose a dosing regimen
- decide whether to initiate therapy with a loading dose
- monitor the patient for toxicity and for therapeutic effect adjust the dose
-

Dose titration may be accomplished by either of two general approaches that differ in dosage and frequency of administration, but reach the same total amount of digoxin accumulated in the body.
1. If rapid titration is considered medically appropriate, administer a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.
2. More gradual titration may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

2.2 Serum Digoxin Concentrations

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication.

Studies have shown diminished efficacy at serum levels < 0.5 ng/mL, while levels above 2 ng/mL are associated with increased toxicity without increased benefit. The inotropic effects of digoxin tend to appear at lower concentrations than the electrophysiological effects. Based on retrospective analysis, adverse events may be higher in the upper therapeutic range.
Perform sampling of serum concentrations just before the next scheduled dose of the drug. If this is not possible, sample at least 6 hours or later after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.
The serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.
When decision-making is to be guided by serum digoxin levels, the clinician must consider the possibility of reported concentrations that have been falsely elevated by endogenous digoxin-like immunoreactive substances *[see Drug Interactions (7.4)]*. If the assay being used is sensitive to these substances, it may be prudent to obtain a baseline measurement before digoxin therapy is started, and correct later values by the reported baseline level.

2.3 Loading Dose

Loading doses for each age group are given in Table 1 below.

In pediatric patients, if a loading dose is needed, it can be administered with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 4- to 8-hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given as the loading dose ***[see Table 1 and 2]***.

Table 1: Estimate the Daily Loading Dose

Age	Daily Oral Loading Dose, mcg/kg/day
Premature	20 - 30
Full-Term	25 - 35
1 to 24 months	35 - 60
2 to 5 years	30 - 45
5 to 10 years	20 - 35
Over 10 years	10 - 15

More gradual attainment of digoxin levels can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in Table 2 (2.4 Estimate of Daily Maintenance Dose) can be used in calculating this dose for patients with normal renal function. Steady state will be attained after approximately 5 days in subjects with normal renal function.

2.4 Estimate of Daily Maintenance Dose

The recommended daily maintenance doses for each age group are given in Table 2 below. These recommendations assume the presence of normal renal function.

Table 2: Estimate of the Daily Maintenance Dose

Age	Daily Oral Maintenance Dose, mcg/kg/day	Oral Maintenance Dose for Twice or Once Daily Dose Regimen, mcg/kg/dose
Premature	4.7 – 7.8	2.3 – 3.9 Twice daily
Full-Term	7.5 – 11.3	3.8 – 5.6 Twice daily
1 to 24 months	11.3 – 18.8	5.6 – 9.4 Twice daily
2 to 5 years	9.4 – 13.1	4.7 – 6.6 Twice daily
5 to 10 years	5.6 – 11.3	2.8 – 5.6 Twice daily
Over 10 years	3.0 – 4.5	3.0 – 4.5 Once daily

Dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, dosage selection

must be based upon clinical assessment and ultimately therapeutic drug level monitoring of the patient.
Divided daily dosing is recommended for pediatric patients under age 10. In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be made as shown in Tables 1 and 2. Renal clearance is further reduced in the premature infant. Beyond the immediate newborn period, pediatric patients generally require proportionally larger doses than adults on the basis of body weight or body surface area. Pediatric patients over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young pediatric patients tolerate slightly higher serum concentrations than do adults. For pediatric patients with known or suspected renal dysfunction, lower starting doses should be considered combined with frequent monitoring of digoxin levels.
NOTE: The calibrated dropper supplied with the 60 mL bottle of digoxin oral solution is not appropriate to measure doses below 0.2 mL. Doses less than 0.2 mL require appropriate methods or measuring devices designed to administer an accurate amount to the patient, such as a graduated syringe.

2.5 Adjustment of Dose

The body's handling of digoxin can be affected by many different patient-specific factors. Some of the possible effects are small, so anticipatory dose adjustment might not be required, but others should be considered before initial dosing *[see Clinical Pharmacology (12.2) and Drug Interactions (7)]*.

Both adults and pediatric patients with abnormal renal function need to have the dose of digoxin proportionally reduced. Recommended maintenance doses based upon lean body weight and renal function are listed in Table 3. Developmental changes in pediatric renal function were factored into Table 3. However, age-related and other changes in adult renal function were not.

The volume of distribution of digoxin is proportional to lean body weight and doses listed in Table 3 assume average body composition. The dose of digoxin must be reduced in patients whose lean weight is an abnormally small fraction of their total body mass because of obesity or edema.

Table 3: Usual Maintenance Dose Requirements (mcg) of Digoxin Based upon Age, Lean Body Weight and Renal Function

Corrected Ccr (mL/min per 70 kg)[a]		Dose to be given **Twice Daily** **< 10 years of age**							Dose to be given **Once Daily** **> 10 years of age and adults**							Number of Days Before Steady State Achieved
		Lean Body Weight							Lean Body Weight							
	kg	**5**	**10**	**20**	**30**	**40**	**50**	**60**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	
	lb	11	22	44	66	88	110	132	88	110	132	154	176	198	220	

10		10	20	40	60	80	100	120	80	100	120	140	160	180	200	19
20		11	23	45	68	90	113	135	90	113	135	158	180	203	225	16
30		13	25	50	75	100	125	150	100	125	150	175	200	225	250	14
40		14	28	55	83	110	138	165	110	138	165	193	220	248	275	13
50		15	30	60	90	120	150	180	120	150	180	210	240	270	300	12
60		16	33	65	98	130	163	195	130	163	195	228	260	293	325	11
70		18	35	70	105	140	175	210	140	175	210	245	280	315	350	10
80		19	38	75	113	150	188	225	150	188	225	263	300	338	375	9
90		20	40	80	120	160	200	240	160	200	240	280	320	360	400	8
100		21	43	85	128	170	213	255	170	213	255	298	340	383	425	7

a. Twice daily dosing is recommended for pediatric patients under 10 years of age. Once daily dosing is recommended for pediatric patients above 10 years of age and adults.

b. Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 – Age)/Scr. For women, this result should be multiplied by 0.85.

Note: This equation cannot be used for estimating creatinine clearance in pediatric patients. For pediatric patients, the modified Schwartz equation may be used as listed below. The formula was based on height in cm and Scr in mg/dL where k is a constant. Ccr is corrected to 1.73 m^2 body surface area. During the first year of life, the value of k is 0.33 for pre-term babies and 0.45 for term infants, The k is 0.55 for pediatric patients and adolescent girls and 0.7 for adolescent boys.

GFR (mL/min/1.73 m2) = (k x Height)/Scr

c. The doses are rounded to whole numbers.

Determination of the target dose in milliliters of Digoxin Oral Solution based on body weight is shown in Table 4. Provided is the volume required per dose, NOT per day.

Table 4: Dose in Milliliters

Target Dose in mcg/kg		**Volume to be given in mL**												
		2	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**30**
Weight in kg ↓	**2**	0.08[b]	0.12[b]	0.16[b]	0.2	0.2	0.3	0.4	0.5	0.6	0.6	0.7	0.8	1.2
	3	0.12[b]	0.18[b]	0.2	0.3	0.4	0.5	0.6	0.7	0.8	1.0	1.1	1.2	1.8
	4	0.16[b]	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6	2.4
	5	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	3.0
	6	0.2	0.4	0.5	0.6	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4	3.6

7	0.3	0.4	0.6	0.7	0.8	1.1	1.4	1.7	2.0	2.2	2.5	2.8	4.2
8	0.3	0.5	0.6	0.8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2	4.8
9	0.4	0.5	0.7	0.9	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6	5.4
10	0.4	0.6	0.8	1.0	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	6.0
11	0.4	0.7	0.9	1.1	1.3	1.8	2.2	2.6	3.1	3.5	4.0	4.4	6.6
12	0.5	0.7	1.0	1.2	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8	7.2
13	0.5	0.8	1.0	1.3	1.6	2.1	2.6	3.1	3.6	4.2	4.7	5.2	7.8
14	0.6	0.8	1.1	1.4	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6	8.4
15	0.6	0.9	1.2	1.5	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0	9.0
20	0.8	1.2	1.6	2.0	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0	12.0
30	1.2	1.8	2.4	3.0	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0	18.0
40	1.6	2.4	3.2	4.0	4.8	6.4	8.0	9.6	11.2	12.8	14.4	16.0	24.0
50	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	14.0	16.0	18	20.0	30.0
60	2.4	3.6	4.8	6.0	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0	36.0
70	2.8	4.2	5.6	7.0	8.4	11.2	14.0	16.8	19.6	22.4	25.2	28.0	42.0
80	3.2	4.8	6.4	8.0	9.6	12.8	16.0	19.2	22.4	25.6	28.8	32.0	48.0
90	3.6	5.4	7.2	9.0	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0	54.0
100	4.0	6.0	8.0	10.0	12.0	16.0	20.0	24.0	28.0	32.0	36.0	40.0	60.0

[a] Recommended dosing regimen for pediatric patients under 10 years of age is twice daily. Recommended dosing regimen for pediatric patients over 10 years of age and adults is once daily.

[b] Use calibrated dropper for measurement. In the case of required volume less than 0.2 mL, a separate device such as a graduated syringe is recommended for adequate measurement.

On the left side of the chart, locate the patient's weight in kilograms. At the top of the chart, identify which dose in mcg/kg will be used for this patient. The block on the chart at which the two rows (weight and target dose) intersect is the milliliter amount that should be given to the patient.

The monitoring described in Section 2.2 may suggest increases or decreases in digoxin doses. Additional monitoring, and in some cases anticipatory dose adjustment, may be indicated around the time of various changes to the patient including:

- normal development through childhood;
- concomitant drug use should be considered when adjusting the estimated digoxin dose *[see Drug Interactions (7)]*;
- new co-administration of an antibiotic, especially if the patient had required high doses of digoxin in order to achieve modest serum concentrations, raising the suspicion that a substantial fraction of administered digoxin was being destroyed by colonic bacteria; and
- changes in renal function [see *Table 3: Usual Maintenance Dose Requirements (mcg) of Digoxin* above].

7. Under **DOSAGE FORMS AND STRENGTHS,** the following **NOTE** was added:
   NOTE: The calibrated dropper supplied with the 60 mL bottle of Digoxin Oral Solution is not appropriate to measure doses below 0.2 mL. Doses less than 0.2 mL require appropriate methods or measuring devices designed to administer an accurate amount to the patient, such as a graduated syringe.

8. Under **CONTRAINDICATIONS** the section was changed from:
   Allergy to digoxin is rare. In such patients (who may or may not have similar reactions to other forms of digitalis), the use of digoxin is contraindicated. Digitalis glycosides are contraindicated in ventricular fibrillation.

   To read as follows:
   Allergy to digoxin is rare. Digoxin is contraindicated in patients with a known hypersensitivity to digoxin or other forms of digitalis. Digitalis glycosides, such as digoxin, are contraindicated in ventricular fibrillation.

9. Under **WARNINGS AND PRECAUTIONS**, section 5.1 title was changed from:
   Use in Patients with Wolff-Parkinson-White Syndrome

   To read as follows:
   Use in Patients with Accessory AV Pathway (Wolff-Parkinson-White Syndrome)

10. Under **WARNINGS AND PRECAUTIONS**, section 5.2 the entire section was reworded, including the title. The section changed from:
    5.2 Use in Patients with Sick Sinus Syndrome
    By slowing conduction in nodal tissue, digoxin administration can exacerbate Sick Sinus Syndrome and can cause a greater degree of atrioventricular block.

    To read as follows:
    5.2 Use in Patients with Sinus Node Disease and AV Block
    Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block particularly in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing

incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

11. Under **WARNINGS AND PRECAUTIONS,** section [redacted] (b) (4)

    In patients with hypertrophic cardiomyopathy (formerly called idiopathic hypertrophic subaortic stenosis), the positive inotropic effect of digoxin leads to an increased subvavular outflow gradient. Digoxin is rarely beneficial in patients with this condition.
    Chronic constrictive pericarditis is not generally associated with any inotropic defect, so heart failure of this etiology is unlikely to respond to treatment with digoxin. By slowing the resting heart rate, digoxin may actually decrease cardiac output in these patients.
    Patients with amyloid heart disease may be more susceptible to toxicity from digoxin.
    Digoxin is of limited value in patients with restrictive cardiomyopathies, although it has been used for rate control in the subgroup of patients with atrial fibrillation.

    To read as follows:

    Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may not benefit by digoxin treatment and may be particularly susceptible to adverse reactions when they are treated with digoxin.

    In patients with hypertrophic cardiomyopathy (formerly called idiopathic hypertrophic subaortic stenosis), the positive inotropic effect of digoxin leads to an increased subvalvular outflow gradient and therefore, may compromise cardiac output. Digoxin is rarely beneficial in patients with this condition.

    Chronic constrictive pericarditis is not generally associated with any inotropic defect, so heart failure of this etiology is unlikely to respond to treatment with digoxin. By slowing the resting heart rate, digoxin may actually decrease cardiac output in these patients.

    Digoxin as an inotropic agent is of limited value in patients with restrictive cardiomyopathies, although it has been used for ventricular rate control in the subgroup of patients with atrial fibrillation. In addition, patients with amyloid heart disease may be more susceptible to toxicity from digoxin at therapeutic levels because of an increased binding of digoxin to extracellular amyloid fibrils.

12. Under **WARNINGS AND PRECAUTIONS**, a new section **5.5 Use in Patients with Impaired Renal Function** was added to read as follows:

    Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin *[see*

Dosage and Administration (2.4)]. Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

13. Under **WARNINGS AND PRECAUTIONS,** section **5.6 Use in Patients with Electrolyte Disorders,** the first sentence was changed from:

    Even at serum levels of digoxin within the conventional therapeutic range (0.5 to 2 ng/mL), the risk of digoxin toxicity is increased by hypokalemia.

    To read as follows:

    In patients with hypokalemia or hypomagnesemia, toxicity may occur at concentrations within therapeutic range because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin.

14. Under **WARNINGS AND PRECAUTIONS,** section **5.8 Use in Thyroid Disorders and Hypermetabolic States,** the following was added as the first paragraph:

    Hypothyrodism may reduce the requirements for digoxin. Heart failure and atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition.

15. Under **WARNINGS AND PRECAUTIONS,** sections 5.9, 5.10 and 5.11 are new and read as follows:

    5.9 Use in Patients with Acute Myocardial Infarction

    In patients with acute myocardial infarction, particularly if they have ongoing ischemia, the use of inotropic drugs, such as digoxin, may result in undesirable increases in myocardial oxygen demand and ischemia. Moreover, the use of digoxin may result in potentially detrimental increases in coronary vascular resistance mediated through alpha adrenergic receptor stimulation.

    5.10 Use in Patients with Myocarditis

    Digoxin can precipitate vasoconstriction and may promote production of pro-inflammatory cytokines. Therefore, avoid digoxin in patients with myocarditis.

    5.11 ECG Changes During Exercise

    The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing that may be indistinguishable from those of ischemia. These electrophysiologic effects

reflect an expected effect of the drug and are not indicative of toxicity. Digoxin does not significantly decrease heart rate during exercise.

16. Under **WARNINGS AND PRECAUTIONS**, old section **5.8 Laboratory Tests** was moved to section **5.12** and reworded to read as follows:

    Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting.

    Assays of serum digoxin levels are described elsewhere *[see Drug Interactions (7.4)]*, as is their use in patient monitoring *[see Dosage and Administration (2.2)]*.

17. Under **ADVERSE REACTIONS,** the subsections were numbered and were changed from:

    Cardiac
    Conduction disturbances or supraventricular tachyarrhythmias, such as atrioventricular (AV) block, atrial tachycardia with or without block and junctional (nodal) tachycardia are the most common arrhythmias associated with digoxin toxicity in children. Ventricular arrhythmias, such as unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are less common. Ventricular tachycardia may result from digitalis toxicity. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmias or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.
    Gastrointestinal
    Anorexia, nausea, vomiting and diarrhea may be early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms.
    CNS
    Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur. These may be difficult to recognize in infants and children. In one reported case, asymmetric chorea was seen at high digoxin levels, and reappeared when similar levels were inadvertently re-achieved.
    Other
    Gynecomastia is occasionally observed.

    To read as follows:

    6.1 Cardiac
    In adults, high doses of digoxin may produce a variety of electrocardiographic changes and rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multifocal ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable.

In pediatric patients, the use of digoxin may produce arrhythmia. The most common are conduction disturbances or supraventricular tachycarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmias or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

6.2 Gastrointestinal

Anorexia, nausea, vomiting and diarrhea may be early symptoms of digoxin toxicity. However, uncontrolled heart failure may also produce such symptoms. The use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

6.3 CNS and Special Senses

Digoxin can produce visual disturbances (blurred vision, green-yellow color disturbances, halo effect), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

6.4 Other

Gynecomastia has been reported following the prolonged use of digoxin. Thrombocytopenia, maculopapular rash and other skin reactions have been observed.

18. Under **DRUG INTERACTIONS**, the entire section was changed from:

7.1 P-Glycoprotein (PGP) Inducers/Inhibitors

Drugs that induce/inhibit P-glycoprotein in intestine or kidney have the potential to alter digoxin pharmacokinetics.

7.2 Antiarrhythmics

In patients receiving digoxin therapy, significant increases in serum digoxin concentrations have been reported with amiodarone, propafenone and quinidine. On initiation of these medications, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued. If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity.

No significant changes in digoxin pharmacokinetics have been reported with disopyramide, dofetilide, flecainide, moricizine, mexilitine, procainamide, or sotalol.

7.3 Calcium Channel Blockers

Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- to-under-digitalization. Whenever over-digitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid under-digitalization. In previous clinical trials with other verapamil formulations related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.
Digoxin levels should be monitored when initiating, adjusting, and discontinuing diltiazem, nifedipine, nitrendipine therapy to avoid possible over- or under-digitalization.
No significant changes in digoxin pharmacokinetics have been reported with amlodipine, felodipine, isradipine, nicardipine, or nisoldipine.

7.4 ACE Inhibitors

In a study of young healthy male subjects no evidence of a direct pharmacokinetic captopril digoxin interaction could be found. Concomitant administration of captopril with digoxin increases serum digoxin concentration (C_{max}) by 58% and exposure (AUC) by 39% in patients with severe (NYHA Class IV) congestive heart failure. No patient developed evidence of digoxin toxicity.
No significant changes in digoxin pharmacokinetics have been reported with benazepril, enalapril, lisinopril, moexipril, perindopril, quinapril, ramipril, or trandolapril.

7.5 Angiotensin-II Blockers

7.5 Angiotensin-II BlockerWhen telmisartan was coadministered with digoxin, increases in median digoxin peak (49%) and in trough plasma concentration (20%) were observed. It is therefore recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.
No significant changes in digoxin pharmacokinetics have been reported with candesartan, eprosartan, irbesartan, losartan, olmesartan, or valsartan.

7.6 Diuretics

Spironolactone increases the plasma concentrations of digoxin by reducing its renal clearance.

No signficant changes in digoxin pharmacokinetics have been reported with torsemide or triamterene.

7.7 Beta Blockers

Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively, in 12 hypertensive patients. In eight children (age 2 weeks to 8 years), the oral clearance of digoxin decreased by 50% with carvedilol.
No signficant changes in digoxin pharmacokinetics have been reported with bisoprolol or esmolol.

7.8 Epoprostenol

In a pharmacokinetic substudy in patients with congestive heart failure receiving digoxin in whom therapy with epoprostenol was initiated, apparent oral clearance values for digoxin were decreased by 15% on the second day of therapy and had returned to baseline value by day 87. Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with epoprostenol, which may be clinically significant in patients prone to digoxin toxicity.
No significant changes in digoxin pharmacokinetics have been reported with aspirin, bosentan, nesiritide, or prazosin.

7.9 Antithrombotic Drugs

No significant changes in digoxin pharmacokinetics have been reported with argatroban and fondaparinux.

7.10 Platelet Aggregation Inhibitors

No significant changes in digoxin pharmacokinetics have been reported with clopidogrel, dipyridamole, or ticlopidine.

7.11 Lipid Lowering Drugs

No significant changes in digoxin pharmacokinetics have been reported with atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, colesevelam, or ezetimibe.

7.12 CNS Drugs

The therapeutic doses of alprazolam do not significantly alter digoxin pharmacokinetics in healthy subjects. However, in older patients significant increases in digoxin exposure have been reported.

No significant changes in digoxin pharmacokinetics have been reported with citalopram, donepezil, escitalopram, galantamine, levetiracetam, paroxetine, rivastigmine, ropinirole, sertraline, tiagabine, topiramate, zaleplon, or zolpidem.

7.13 Nonsteroidal Antiinflammatory Drugs

Diclofenac and indomethacin have been reported to elevate digoxin levels. Patients should be monitored for possible digoxin toxicity.
No significant changes in digoxin pharmacokinetics have been reported with rofecoxib.

7.14 Antifungal Drugs

Ketoconazole and itraconazole have been reported to elevate plasma concentrations of digoxin.
No significant changes in digoxin pharmacokinetics have been reported with terbinafine or voriconazole.

7.15 Antisecretory Drugs

In normal subjects, co-administration of rabeprazole 20 mg QD resulted in an increase in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Patients may need to be monitored when digoxin is taken concomitantly with rabeprazole.
Lansoprazole, esomeprazole, and omeprazole inhibit gastric acid secretion and may interfere with the absorption of digoxin.
No significant changes in digoxin pharmacokinetics have been reported with pantoprazol.

7.16 Antibacterial Drugs

Few cases of elevated serum concentrations of digoxin have been reported in patients receiving digoxin and gatifloxacin. Although dose adjustments for digoxin are not warranted with initiation of gatifloxacin treatment, patients taking digoxin should be monitored for signs and symptoms of toxicity. In patients who display signs and symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate.
Elevated digoxin concentrations have been reported in patients receiving clarithromycin and digoxin concomitantly due to inhibition of intestinal and renal P-glycoprotein. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.
Azithromycin, erythromycin and tetracycline have also been reported to elevate digoxin levels.
No significant changes in digoxin pharmacokinetics have been reported with gemifloxacin, levofloxacin, moxifloxacin, or trovafloxacin.

7.17 Antitubercular Drugs

Rifampin may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. Rifampin reduced the oral bioavailability of digoxin from 63% to 44% in healthy volunteers mainly by inducing P-glycoprotein in the small intestine.

7.18 Antiviral Drugs

Physical incompatibility has been reported with digoxin. Digoxin should not be administered concurrently via the same catheter.
No significant changes in digoxin pharmacokinetics have been reported with famciclovir or valacyclovir.

7.19 Glucose Lowering Drugs

Acarbose has been shown to decrease the bioavailability of digoxin when they are co-administered, which may require digoxin dose adjustment.
In healthy volunteers, co-administration of 50 mg or 100 mg miglitol and digoxin reduced the average plasma concentrations of digoxin by 19% and 28%, respectively. However, in diabetic patients under treatment with digoxin, plasma digoxin concentrations were not altered by co-administration of miglitol 100 mg for 14 days.
No significant changes in digoxin pharmacokinetics have been reported with nateglinide, repaglinide, pioglitazone, or rosiglitazone.

7.20 Immunosuppressive Drugs

Reduced clearance and apparent volume of distribution of digoxin has been observed when coadministered with cyclosporine. Severe digitalis toxicity has been seen within days of starting cyclosporine.
No significant changes in digoxin pharmacokinetics have been reported with sirolimus.

7.21 Drugs for Benign Prostatic Hyperplasia

No significant changes in digoxin pharmacokinetics have been reported with alfuzosin, dutasteride, finasteride, or tamsulosin.

7.22 Drugs for Respiratory Disorders

Albuterol and salbutamol have been reported to lower serum digoxin levels. Nevertheless, it would be prudent to evaluate carefully the serum digoxin levels.
No significant changes in digoxin pharmacokinetics have been reported with montelukast.

7.23 Drugs Interfering with Absorption

Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Activated charcoal, antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, certain anticancer drugs, metoclopramide, meals high in bran, sucralfate may interfere with digoxin absorption, resulting in unexpectedly low serum concentrations.
Colestipol can bind digoxin. Discontinuing colestipol hydrochloride could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking colestipol hydrochloride.

7.24 Dietary Products

Grapefruit juice had no significant effect on the maximum plasma drug concentration (C_{max}) of digoxin (0.5 mg) or the overall exposure. The digoxin renal clearance remained unchanged.

7.25 Herbal Products

Administration of St. John's Wort extract to 8 healthy male volunteers during 14 days resulted in a 18% decrease in exposure (AUC) after a single digoxin dose (0.5 mg) due to 1.4-fold increase in duodenal P-glycoprotein activity.

7.26 Other Digoxin-Drug Interaction Information

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity. Doxazosin, ketorolac, meloxicam, and mycophenolate have no effect on protein binding of digoxin. *In vitro* studies indicated that ertapenem had no effect on P-glycoprotein transport of digoxin. As a cationic drug that is eliminated by renal tubular secretion, digoxin has the potential for interaction with metformin by competing for common renal tubular transport systems.
There have been inconsistent reports regarding the effects of other drugs (e.g., penicillamine, quinine) on serum digoxin concentration.
No significant changes in digoxin pharmacokinetics have been reported with acitretin, aprepitant, orlistat, raloxifene, sevelamer, or tegaserod.

7.27 Drug-Laboratory Test Interaction

Endogenous substances of unknown composition (digoxin-like immunoreactive substances, DLIS) can interfere with standard radioimmunoassays for digoxin. The interference most often causes results to be falsely positive or falsely elevated, but sometimes it causes results to be falsely reduced. Some assays are more subject to these failings than others. An LC/MS/MS method is available that may provide a more accurate determination of plasma digoxin levels, however, clinical trials have not been conducted to determine its susceptibility to DLIS interference. DLIS are present in up to half of all neonates and in varying percentages of pregnant women, patients with hypertrophic cardiomyopathy, patients with renal or hepatic dysfunction, and other patients who are volume-

expanded for any reason. The measured levels of DLIS (as digoxin equivalents) are usually low (0.2 to 0.4 ng/mL), but sometimes they reach levels that would be considered therapeutic or even toxic.
In some assays spironolactone may be falsely detected as digoxin, at levels up to 0.5 ng/mL. Some traditional Chinese medicines cause similar interference.
Spironolactone and DLIS are much more extensively protein-bound than digoxin. As a result, assays of free digoxin levels (which tend to be about 25% less than total levels, consistent with the usual extent of protein binding) are not affected by spironolactone or DLIS.

7.28 Pharmacodynamic Interactions

Dofetilide
In patients, the concomitant administration of digoxin with dofetilide was associated with a higher rate of Torsade de pointes.
Moricizine
Moricizine has been reported to increase the PR interval and QRS duration. There are reports of first-degree atrioventricular block or bundle branch block developing in patients with concomitant digitalis administration. The known effects of moricizine on calcium conductance may explain the effects on atrioventricular node conduction.
Sotalol
Proarrhythmic events were more common in sotalol treated patients also receiving digoxin; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.
Teriparatide
Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, teriparatide should be used with caution in patients taking digitalis.
Potassium-depleting corticosteroids and diuretics may be major contributing factors to digitalis toxicity.
Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients.
Treatment of hypothyroidism in patients taking digoxin may increase the dose requirements of digoxin. Thyroid administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin.
Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias.
Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients.
Although β-adrenergic blockers or calcium-channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.
Due to considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently.
Furthermore, caution should be exercised when combining digoxin with any drug

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

To read as follows:

7.1 P-Glycoprotein (PGP) Inducers/Inhibitors

Digoxin is a substrate for P-glycoprotein, at the level of intestinal absorption, renal tubular section and biliary-intestinal secretion. Therefore, drugs that induce/inhibit P-glycoprotein have the potential to alter digoxin pharmacokinetics.

7.2 Pharmacokinetic Drug Interactions on Serum Digoxin Levels in Adults

Digoxin concentrations increased > 50%			
	Digoxin Serum Concentration Increase	Digoxin AUC Increase	**Recommendations**
Amiodarone	70%	NA	Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 30% to 50% and continue monitoring.
Captopril	58%	39%	
Nitrendipine	57%	15%	
Propafenone	35-85%	NA	
Quinidine	100%	NA	
Ranolazine	87%	88%	
Ritonavir	NA	86%	
Verapamil	50-75%	NA	
Digoxin concentrations increased < 50%			
Carvedilol	16%	14%	Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 15% to 30% and continue monitoring.
Diltiazem	20%	NA	
Nifedipine	45%	NA	
Rabeprazole	29%	19%	
Telmisartan	20%	NA	
Digoxin concentrations increased, but magnitude is unclear			
Alprazolam, Azithromycin, Clarithromycin, Cyclosporine, Diclofenac, Diphenoxylate, Epoprostenol, Erythromycin, Esomeprazole, Indomethacin, Itraconazole, Ketoconazole, Lansoprazole, Metformin, Omeprazole, Propantheline, Spironolactone, Tetracycline			Measure serum digoxin concentrations before initiating concomitant drugs. Continue monitoring and reduce digoxin dose as necessary.
Digoxin concentrations decreased			

Acarbose, Activated Charcoal, Albuterol, Antacids, Anti-cancer drugs, Cholestyramine, Colestipol, Exenatide, Kaolin-pectin, Meals High in Bran, Metoclpramide, Miglitol, Neomycin, Rifampin, Salbutamol, St. John's Wort, Sucralfate, Sulfasalazine	Measure serum digoxin concentrations before initiating concomitant drugs. Continue monitoring and increase digoxin dose by approximately 20% to 40% as necessary.
No significant Digoxin concentrations changes	
Please refer to section 12.3 for a complete list of drugs which were studied but reported no significant changes on digoxin exposure.	No additional actions are required.

NA – Not available/reported

7.3 Pharmacodynamic Drug Interactions

Antiarrthymics	Dofetilide	Concomitant administration with digoxin was associated with a higher rate of torsade de pointes.
	Moricizine	Reported to increase PR interval and QRS duration. There are reports of first degree atrioventricular block or bundle branch block developing with digitalis administration. The known effects of moricizine on calcium conductance may explain the effects on atrioventricular node conduction.
	Sotalol	Proarrhythmic events were more common in patients receiving sotalol and digoxin than on either alone; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digoxin.
Parathyroid Hormone Analog	Teriparatide	Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Teriparatide transiently increases serum calcium.
Thyroid Supplement	Thyroid	Treatment of hypothyroidism in patients taking digoxin may increase the dose requirements of digoxin.
Sympathomimetics	Epinepherine Norepinephrine Dopamine	Can increase the risk of cardiac arrhythmias.
Neuromuscular Blocking Agents	Succinylcholine	May cause sudden extrusion of potassium from muscle cells causing arrhythmias in patients taking digoxin.

Supplements	Calcium	If administered rapidly by intravenous route, can produce serious arrhythmias in digitalized patients.
Beta-adrenergic blockers and calcium channel blockers	Additive effects on AV node conduction can result in complete heart block.	

7.4 Drug-Laboratory Test Interaction

Endogenous substances of unknown composition (digoxin-like immunoreactive substances, DLIS) can interfere with standard radioimmunoassays for digoxin. The interference most often causes results to be falsely positive or falsely elevated, but sometimes it causes results to be falsely reduced. Some assays are more subject to these failings than others. Several LC/MS/MS methods are available that may provide less susceptibility to DLIS interference. DLIS are present in up to half of all neonates and in varying percentages of pregnant women, patients with hypertrophic cardiomyopathy, patients with renal or hepatic dysfunction, and other patients who are volume-expanded for any reason. The measured levels of DLIS (as digoxin equivalents) are usually low (0.2 to 0.4 ng/mL), but sometimes they reach levels that would be considered therapeutic or even toxic.

In some assays, spironolactone, canrenone and potassium canrenoate may be falsely detected as digoxin, at levels up to 0.5 ng/mL. Some traditional Chinese and Ayurvedic medicine substances like Chan Su, Siberian Ginseng, Asian Ginseng, Ashwagandha or Dashen, can cause similar interference.

Spironolactone and DLIS are much more extensively protein-bound than digoxin. As a result, assays of free digoxin levels in protein-free ultrafiltrate (which tend to be about 25% less than total levels, consistent with the usual extent of protein binding) are less affected by spironolactone or DLIS. It should be noted that ultrafiltration does not solve all interference problems with alternative medicines. The use of an LC/MS/MS method may be the better option according to the good results it provides, especially in term of specificity and limit of quantization.

19. Under USE IN SPECIFIC POPULATIONS, section 8.2 was added to read as follows:

8.2 Labor and Delivery

There is not enough data from clinical trials to determine the safety and efficacy of digoxin during labor and delivery.

20. Under **USE IN SPECIFIC POPULATIONS,** section **8.3 Nursing Mothers** was changed from:

Digoxin levels in human milk are lower than those in maternal serum. A human infant ingesting plausible quantities of such milk will receive much less than therapeutic doses of digoxin, even when the mother's levels are well into the toxic range.

To read as follows:

Digoxin levels in human milk are lower than those in maternal serum. The estimated exposure that a nursing infant would be expected to receive via breastfeeding would be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

21. Under **USE IN SPECIFIC POPULATIONS,** section **8.4 Pediatric Use** was changed from:

Digoxin increases myocardial contractility in children with congestive heart failure. There are no controlled randomized studies of digoxin in children with atrial tachyarrhythmias. [See (b) (4) DOSAGE AND ADMINISTRATION (b) (4)].

To read as follows:

Digoxin increases myocardial contractility in pediatric patients with congestive heart failure. There are no clinical efficacy studies demonstrating benefit in pediatric patients with heart failure. There are no controlled randomized studies of digoxin in pediatric patients with atrial tachyarrhythmias *[see Clinical Studies (14.2)].*

22. Under **USE IN SPECIFIC POPULATIONS,** section **8.5 Geriatric Use** was changed from:

Clinical studies of digoxin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

To read as follows:

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function *[see Dosage and Administration (2.4)].*

23. Under **USE IN SPECIFIC POPULATIONS,** section 8.10 and 8.11 were added to read as follows:

8.10 Race

Race differences in digoxin pharmacokinetics have not been formally studied, but are not expected.

8.11 Malabsorption

The absorption of digoxin is reduced in some malabsorption conditions such as chronic diarrhea.

24. Under **OVERDOSAGE,** the entire section was rewritten from:

Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.
Potassium salts may be used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 1 to 1.5 mEq K^+ per kilogram (kg) body weight may be given provided renal function is adequate (1 gram of potassium chloride contains 13.4 mEq K^+). When correction of the arrhythmia with potassium is urgent and the serum potassium concentration is low or normal, approximately 0.5 mEq/kg of potassium per hour may be given intravenously in 5% dextrose injection. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants care must be taken to avoid intravenous fluid overload. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.
Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.
Because of its large extravascular volume of distribution, digoxin is not effectively removed from the body by dialysis, by exchange transfusion, or during cardiopulmonary bypass.
Multiple doses of activated charcoal have been found effective in at least 1 case report, and may be of use while the need for and availability of digoxin specific antibody fragments are being assessed. In advanced heart block, temporary ventricular pacing may be beneficial.
Digoxin Immune Fab (Ovine) [DIGIBIND®, DIGIFAB®] may be indicated for the treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose.

To read as follows:

10.1 Clinical Manifestations

In adults, the signs and symptoms of toxicity are similar to those described in *Adverse Reactions (6)* but may be more frequent and severe. The most common signs and symptoms of digoxin toxicity are nausea, vomiting, anorexia, and fatigue that occur in 30 to 70% of patients who are overdosed. Extremely high serum concentrations produce hyperkalemia especially in patients with impaired

renal function. Almost every type of cardiac arrhythmia has been associated with digoxin overdose and multiple rhythm disturbances in the same patient are common. Peak cardiac effects occur 3 to 6 hours following ingestion and may persist for 24 hours or longer. Arrhythmias that are considered more characteristic of digoxin toxicity are new-onset Mobitz type 1 A-V block, accelerated junctional rhythms, non-paroxysmal atrial tachycardia with A-V block, and bi-directional ventricular tachycardia. Cardiac arrest from asystole or ventricular fibrillation is usually fatal.

Digoxin toxicity is related to serum concentration. As serum levels increase above 1.2 ng/mL there is a potential for increase in adverse events. The effect on adverse events is enhanced by lower potassium levels. In adults with heart disease, clinical observations suggest that an overdose of digoxin of 10 to 15 mg results in death of half of patients. A dose above 25 mg ingested by an adult without heart disease appeared to be uniformly fatal if no Digoxin Immune Fab (DIGIBIND®, DIGIFAB®) was administered.

In pediatric patients, signs and symptoms of toxicity can occur during or shortly after the dose of digoxin. Frequent non-cardiac effects are similar to those observed in adults although nausea and vomiting are not seen frequently in infants and small pediatric patients. Other reported manifestations of overdose are weight loss in older age groups, failure to thrive in infants, abdominal pain caused by mesenteric artery ischemia, drowsiness, and behavioral disturbances including psychotic episodes. Arrhythmias and combinations of arrhythmias that occur in adult patients can also occur in pediatric patients although sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen less frequently in pediatric patients. Pediatric patients are more likely to develop A-V conduction disturbances, or sinus bradycardia. Any arrhythmia in a child treated with digoxin should be considered related to digoxin until otherwise ruled out. In pediatric patients aged 1 to 3 years without heart disease, clinical observations suggest that an overdose of digoxin of 6 to 10 mg would result in death of half of the patients. In the same population, a dose above 10 mg resulted in death if no Digoxin Immune Fab (DIGIBIND®, DIGIFAB®) was administered.

10.2 Management of Toxicity

Chronic Overdose

If there is suspicion of toxicity, digoxin should be discontinued and the patient placed on a cardiac monitor. Contributing factors such as electrolyte abnormalities, thyroid dysfunction, and concomitant medications should be corrected *[see Dosage and Administration (2.5)]*. Hypokalemia should be corrected by administering potassium so that serum potassium is maintained between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and serum potassium concentration is low, potassium may be administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. Potassium

salts should be avoided in patients with bradycardia or heart block. Symptomatic arrhythmias may be treated with Digoxin Immune Fab (DIGIBIND®, DIGIFAB®).

Acute Overdose

Patients who have intentionally or accidently ingested massive doses of digoxin should receive activated charcoal orally or by nasogastric tube regardless of the time since ingestion since digoxin recirculates to the intestine by enterohepatic circulation. In addition to cardiac monitoring, digoxin should be temporarily discontinued until the adverse reaction resolves. Factors that may be contributing to the adverse reactions should also be corrected *[see Warnings and Precautions (5)]* . In particular, hypokalemia and hypomagnesemia should be corrected. Digoxin is not effectively removed from the body by dialysis because of its large extravascular volume of distribution. Life threatening arrhythmias (ventricular tachycardia, ventricular fibrillation, high degree A-V block, bradyarrhythma, sinus arrest) or hyperkalemia require administration of Digoxin Immune Fab (DIGIBIND®, DIGIFAB®). Digoxin Immune Fab has been shown to be 80-90% effective in reversing signs and symptoms of digoxin toxicity. Bradycardia and heart block caused by digoxin are parasympathetically mediated and respond to atropine. A temporary cardiac pacemaker may also be used. Ventricular arrhythmias may respond to lidocaine or phenytoin. When a large amount of digoxin has been ingested, especially in patients with impaired renal function, hyperkalemia may be present due to release of potassium from skeletal muscle. In this case, treatment with Digoxin Immune Fab (DIGIBIND®, DIGIFAB®) is indicated, an initial treatment with glucose and insulin may be needed if the hyperkalemia is life-threatening. Once the adverse reaction has resolved, therapy with digoxin may be reinstituted following a careful reassessment of dose.

25. Under **CLINICAL PHARMACOLOGY,** the second paragraph of section **12.1 Mechanism of Action** was changed from:

    The cardiologic consequences of these direct and indirect effects are an increase in the force and velocity of myocardial systolic contraction (positive inotropic action), a slowing of the heart rate (negative chronotropic effect), and decreased conduction velocity through the AV node.

To read as follows:

    The cardiologic consequences of these direct and indirect effects are an increase in the force and velocity of myocardial systolic contraction (positive inotropic action), a slowing of the heart rate (negative chronotropic effect), decreased conduction velocity through the AV node, and a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect).

26. Under **CLINICAL PHARMACOLOGY, section 12.2 Pharmacodynamics** was created from the last paragraph of section **12.1 Mechanism of Action**:

    12.2 Pharmacodynamics

Short- and long-term treatment with digoxin slows heart rate, increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

27. Under **CLINICAL PHARMACOLOGY**, section **12.3 Pharmacokinetics** subsection *Distribution*, the third sentence was change from:

Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its sites of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations.

To read as follows:

Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its sites of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects.

28. Under **CLINICAL PHARMACOLOGY**, section **12.3 Pharmacokinetics** subsection *Metabolism*, the first and second sentences were change from:

Only a small percentage of digoxin is metabolized. The end metabolites, which include 3-β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to form via hydrolysis, oxidation, and conjugation.

To read as follows:

Sixteen percent of digoxin is metabolized. The end metabolites include 3-β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates.

29. Under **CLINICAL PHARMACOLOGY**, section **12.3 Pharmacokinetics** subsection *Excretion*, the following was added after the first sentence:

Elimination of digoxin follows first order kinetics.
Following intravenous administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate.

30. Under **CLINICAL PHARMACOLOGY**, section **12.3 Pharmacokinetics** a *Drug-drug Interactions* subsection was added to read as follows:

Based on literature reports no significant changes in digoxin exposure was reported when digoxin was co-administered with the following drugs: alfuzosin, aliskiren, amlodipine, aprepitant, argatroban, aspirin, atorvastatin, benazepril, bisoprolol, black cohosh, bosentan, candesartan, citalopram, clopidogrel, colesevelam, dipyridamole, disopyramide, donepezil, doxazosin, dutasteride, echinacea, enalapril, eprosartan, ertapenem, escitalopram, esmolol, ezetimibe, famciclovir, felodipine, finasteride, flecainide, fluvastatin, fondaparinux, galantamine, gemifloxacin, grapefruit juice, irbesartan, isradipine, ketorlac,

levetiracetam, levofloxacin, lisinopril, losartan, lovastatin, meloxicam, mexilitine, midazolam, milk thistle, moexipril, montelukast, moxifloxacin, mycophenolate, nateglinide, nesiritide, nicardipine, nisoldipine, olmesartan, orlistat, pantoprazole, paroxetine, perindopril, pioglitazone, pravastatin, prazosin, procainamide, quinapril, raloxifene, ramipril, repaglinide, rivastigmine, rofecoxib, ropinirole, rosiglitazone, rosuvastatin, sertraline, sevelamer, simvastatin, sirolimus, solifenacin, tamsulosin, tegaserod, terbinafine, tiagabine, ticlopidine, tigecycline, topiramate, torsemide, tramadol, trandolapril, triamterene, trospium, trovafloxacin, valacyclovir, valsartan, varenicline, voriconazole, zaleplon, zolpidem.

31. Under **NONCLINICAL TOXICOLOGY**, the section was changed from:

There have been no long-term studies performed in animals to evaluate carcinogenic potential.

To read as follows:

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

32. Under **CLINICAL STUDIES,** section **14.2 Atrial Fibrillation,** the second paragraph was moved to be the first sentence and modified to read as:

Digoxin has also been studied as a means of controlling the ventricular response to chronic atrial fibrillation in adults. Digoxin reduced the resting heart rate, but not the heart rate during exercise.

33. Section **17 PATIENT COUNSELING,** is a new section added as follows:

Patients receiving digoxin should be given the following instructions by the physician.

- Advise patients that digoxin is a cardiac glycoside used to treat heart failure and heart arrhythmias. Digoxin helps the heart beat more efficiently in adults and pediatric patients and decreases the heart rate at rest during abnormal rhythms in adults.
- Instruct patients to take this medication as directed by their physician. The dose of digoxin should not be adjusted without consulting with a physician or other healthcare professional.
- Advise patients that many drugs can interact with digoxin. Patients should be instructed to inform their doctor and pharmacist if they are taking any over the counter medications, including herbal medication, or are started on a new prescription.
- The patient should be made aware that blood tests will be necessary to ensure that their digoxin dose is appropriate for them.
- Advise patients to contact their doctor or a health care professional if they experience nausea, vomiting, persistent diarrhea, confusion, weakness, or visual disturbances (including blurred vision, green-yellow color

disturbances, halo effect) as these could be signs that the dose of digoxin may be too high..

- Advise parents or caregivers that the symptoms of having too high digoxin doses may be difficult to recognize in infants and pediatric patients. Symptoms such as weight loss, failure to thrive in infants, abdominal pain, and behavioral disturbances may be indications of digoxin toxicity.
- Suggest to the patient to monitor and record their heart rate and blood pressure daily.
- Instruct patients to use the calibrated dropper to measure their digoxin dose and to avoid less precise measuring tools, such as teaspoons. For doses less than 0.2 mL, another measuring syringe should be provided to the patient for accurate dosing, since the provided calibrated dropper is not appropriate to measure doses less than 0.2 mL.
- Instruct women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiation or continuing therapy with digoxin.

Conclusion:
The Division and Sponsor agreed with the wording as noted above An approval letter for supplement 004 will be drafted for Dr. Southworth's signature.

Alexis Childers
Regulatory Health Project Manager

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/s/

ALEXIS T CHILDERS
09/22/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021648Orig1s004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Alexis Childers/RPM/ODE1/DCRP/301-796-0442

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
9/1/11		NDA 21648	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
digoxin	standard	Cardiac glycoside	September 13, 2011

NAME OF FIRM:	
Roxane Laboratories, Inc	PDUFA Date: NA label review was due last October 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☑ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☑ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☑ LABELING REVISION

EDR link to submission: link to original submission: \\FDSWA150\NONECTD\N21648\S_004\2010-10-05

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

The Division had major revisions to clin pharm sections. Both the Division and Sponsor have agreed to all recommended changes. A clean copy will be emailed

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	☑ eMAIL ☐ HAND

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/s/

ALEXIS T CHILDERS
09/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21648/S-004 **PRIOR APPROVAL SUPPLEMENT**

Roxane Laboratories, Inc.
Attention: Ms. Elizabeth A. Ernst
Director, Drug Regulatory Affairs & Medical Affairs
1809 Wilson Rd.
Columbus, OH 43228

Dear Ms. Ernst:

We have received your June 11, 2010 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Digoxin Elixir USP, 0.05 mg/mL

NDA Number: 21648

Supplement number: 004

Date of supplement: June 11, 2010

Date of receipt: June 14, 2010

This supplemental application, submitted as a labeling supplement, proposes to provide draft updated labeling for Digoxin Elixir.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 13, 2010 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, please contact:

Ms. Alexis Childers
Regulatory Health Project Manager
(301) 796-0442

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21648	SUPPL-4	ROXANE LABORATORIES INC	DIGOXIN ELIXIR 0.05MG/ML

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/s/

DANIEL BRUM
06/22/2010
Signed on behalf of Edward Fromm