CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-282

Approval Letter

ANDA 40-282

DEC 23 1999

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
Director, Regulatory Affairs
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated October 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Digoxin Tablets USP, 0.125 mg and 0.25 mg.

Reference is also made to your amendments dated January 28, February 22, March 18, March 26, August 11, November 12, November 24, and December 21, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Digoxin Tablets USP, 0.125 mg and 0.25 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lanoxin® Tablets, 0.125 mg and 0.25 mg, respectively, of Glaxo Wellcome, Inc). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 10/13/99

Roger L. Williams, M.D
Director, Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-282

FINAL PRINTED LABELING

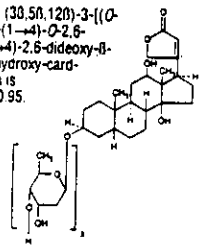
PRODUCT INFORMATION

LANOXIN® (digoxin) Tablets, USP

125 mcg (0.125 mg) Scored
I.D. Imprint Y3B (yellow)
250 mcg (0.25 mg) Scored
I.D. Imprint X3A (white)

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

Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$, its molecular weight is 780.95, and its structural formula is:



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

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

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

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

Table 1: Comparisons of the Systemic Availability and Equivalent Doses for Oral Preparations of LANOXIN

Product	Absolute Bioavailability	Equivalent Doses (mcg)* Among Dosage Forms			
LANOXIN Tablets	60 - 80%	62.5	125	250	500
LANOXIN Elixir Pediatric	70 - 85%	62.5	125	250	500
LANOXICAPS®	90 - 100%	50	100	200	400
LANOXIN Injection/IV	100%	50	100	200	400

* For example, 125-mcg LANOXIN Tablets equivalent to 125 mcg LANOXIN Elixir Pediatric equivalent to 100 mcg LANOXICAPS® equivalent to 100 mcg LANOXIN Injection/IV.

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

LANOXIN Elixir Pediatric equivalent to 100 mcg LANOXICAPS® equivalent to 100 mcg LANOXIN Injection/IV.

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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. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum 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: Serum Digoxin Concentrations).

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 best with lean (i.e., ideal) body weight, not total body weight.

Metabolism: Only a small percentage (16%) of a dose 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 be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion: Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to 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 and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

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

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

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

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

Table 2: Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of LANOXIN

Product	Time to Onset of Effect*	Time to Peak Effect*
LANOXIN Tablets	0.5 - 2 hours	2 - 6 hours
LANOXIN Elixir Pediatric	0.5 - 2 hours	2 - 6 hours
LANOXICAPS	0.5 - 2 hours	2 - 6 hours
LANOXIN Injection/IV	5 - 30 minutes†	1 - 4 hours

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

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

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

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6,800 patients with heart failure and left ventricular ejection fraction ≤ 0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or LANOXIN, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91 to 1.07). LANOXIN was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

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patient having at least one hospitalization for heart failure,
reduction in total hospitalizations (for any cause).

Use of LANOXIN was associated with a trend in reductic
all-cause death or hospitalization. The trend was evident in
of patients with mild heart failure as well as more severe di
shown in Table 3. Although the effect on all-cause death or
ization was not statistically significant, much of the appare
derived from effects on mortality and hospitalization attribu
failure.

**Table 3: Subgroup Analyses of Mortality and Hospita
During the First Two Years Following Randomizat**

		Risk of All-Cause Mortality or All-Cause Hospitalization*			Risk of HF- Mortalit HF-Related Hos	
	n	Placebo	LANOXIN	Relative risk†	Placebo	LANOXI
All patients (EF ≤ 0.45)	6801	604	593	0.94 (0.88-1.00)	294	217
NYHA I/II	4571	549	541	0.96 (0.89-1.04)	242	178
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)	244	190
CTR ≤0.55	4455	561	563	0.98 (0.91-1.06)	239	180
NYHA III / IV	2224	719	696	0.88 (0.80-0.97)	402	295
EF <0.25	2258	677	637	0.84 (0.76-0.93)	394	270
CTR >0.55	2346	687	650	0.85 (0.77-0.94)	398	287
EF >0.45‡	987	571	585	1.04 (0.88-1.23)	179	136

* Number of patients with an event during the first 2 years
randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

In situations where there is no statistically significant ben
treatment evident from a trial's primary endpoint, results pe
a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation: In patients with chronic atrial
digoxin slows rapid ventricular response rate in a linear dos
response fashion from 0.25 to 0.75 mg/day. Digoxin should
used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE:

Heart Failure: LANOXIN is indicated for the treatment of mil
erate heart failure. LANOXIN increases left ventricular ejectio
and improves heart failure symptoms as evidenced by exerc
ity and heart failure-related hospitalizations and emergency c
having no effect on mortality. Where possible, LANOXIN sho
used with a diuretic and an angiotensin-converting enzyme i
but an optimal order for starting these three drugs cannot be
specified.

Atrial Fibrillation: LANOXIN is indicated for the control of ve
response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS: Digitalis glycosides are contraindicat
patients with ventricular fibrillation or in patients with a know
sensitivity to digoxin. A hypersensitivity reaction to other dig
preparations usually constitutes a contraindication to digoxin

WARNINGS:

Sinus Node Disease and AV Block: Because digoxin slows s
and AV conduction, the drug commonly prolongs the PR inte
drug may cause severe sinus bradycardia or sinoatrial block
patients with pre-existing sinus node disease and may cause
advanced or complete heart block in patients with pre-existin
plete AV block. In such patients consideration should be give
insertion of a pacemaker before treatment with digoxin.

Accessory AV Pathway (Wolff-Parkinson-White Syndrome):
intravenous digoxin therapy, some patients with paroxysmal
rillation or flutter and a coexisting accessory AV pathway hav
oped increased antegrade conduction across the accessory p
bypassing the AV node, leading to a very rapid ventricular res
ventricular fibrillation. Unless conduction down the accessory
has been blocked (either pharmacologically or by surgery), di
should not be used in such patients. The treatment of paroxy-
supraventricular tachycardia in such patients is usually direct
cardioversion.

Use in Patients with Preserved Left Ventricular Systolic Fur
Patients with certain disorders involving heart failure associat
preserved left ventricular ejection fraction may be particularly
tible to toxicity of the drug. Such disorders include restrictive
diomyopathy, constrictive pericarditis, amyloid heart disease,
acute cor pulmonale. Patients with idiopathic hypertrophic sul
stenosis may have worsening of the outflow obstruction due t
inotropic effects of digoxin.

PRECAUTIONS:

Use in Patients with Impaired Renal Function: Digoxin is pri
excreted by the kidneys; therefore, patients with impaired rena
tion require smaller than usual maintenance doses of digoxin
DOSAGE AND ADMINISTRATION). Because of the prolonged
tion half-life, a longer period of time is required to achieve an
new steady-state serum concentration in patients with renal in
ment than in patients with normal renal function. If appropriat
not taken to reduce the dose of digoxin, such patients are at h
for toxicity, and toxic effects will last longer in such patients th
patients with normal renal function.

Use in Patients with Electrolyte Disorders: In patients with
hypokalemia or hypomagnesemia, toxicity may occur despite
digoxin concentrations below 2.0 ng/mL, because potassium
nesium depletion sensitizes the myocardium to digoxin. There
is desirable to maintain normal serum potassium and magnes
concentrations in patients being treated with digoxin. Deficienc
these electrolytes may result from malnutrition, diarrhea, or pr
vomiting, as well as the use of the following drugs or procedu
diuretics, amphotericin B, corticosteroids, antacids, dialysis, a
mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to di
toxicity. Calcium, particularly when administered rapidly by the
venous route, may produce serious arrhythmias in digitalized p
On the other hand, hypocalcemia can nullify the effects of digo
humans, thus digoxin may be partia

...heart failure 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.

Use in Patients with Electrolyte Disorders: In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL, 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. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

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

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

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

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

Laboratory Test Monitoring: 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. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section.

Drug Interactions: Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam,* and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result (see CLINICAL PHARMACOLOGY: Absorption). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs,* and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs [e.g., *quinine, penicillamine*] on serum digoxin concentration. *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 beta-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 advanced or complete heart block.

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

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

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.

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 a pregnant woman or can affect reproductive capacity. Digoxin should be given to a pregnant woman only if clearly needed.

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

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

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).

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

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

Adults: ***Cardiac:*** Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of 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 multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

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

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

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

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

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

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

Infants and Children: The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of

digoxin may produce anorexia, nausea, vomiting, diarrhea, and disturbances in young patients, these are rarely the initial symp of overdosage. Rather, the earliest and most frequent manifesta excessive dosing with digoxin in infants and children is the app ance of cardiac arrhythmias, including sinus bradycardia. In chi the use of digoxin may produce any arrhythmia. The most com are conduction disturbances or supraventricular tachyarrhythmi such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. bradycardia may be a sign of impending digoxin intoxication, es cially in infants, even in the absence of first-degree heart block. arrhythmia or alteration in cardiac conduction that develops in a taking digoxin should be assumed to be caused by digoxin, unti ther evaluation proves otherwise.

OVERDOSAGE:

Treatment of Adverse Reactions Produced by Overdosage: Dig should be temporarily discontinued until the adverse reaction re Every effort should also be made to correct factors that may cor tribute to the adverse reaction (such as electrolyte disturbances concurrent medications). Once the adverse reaction has resolve therapy with digoxin may be reinstituted, following a careful rea ment of dose.

Withdrawal of digoxin may be all that is required to treat the a reaction. However, when the primary manifestation of digoxin o dosage is a cardiac arrhythmia, additional therapy may be neede

If the rhythm disturbance is a symptomatic bradyarrhythmia heart block, consideration should be given to the reversal of tox with DIGIBIND® [Digoxin Immune Fab (Ovine)] (see below), the atropine, or the insertion of a temporary cardiac pacemaker. Ho asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac moni of the patient.

If the rhythm disturbance is a ventricular arrhythmia, consider should be given to the correction of electrolyte disorders, particu hypokalemia (see below) or hypomagnesemia is present. DIGIBI a specific antidote for digoxin and may be used to reverse poten life-threatening ventricular arrhythmias due to digoxin overdosa

Administration of Potassium: Every effort should be made to tain the serum potassium concentration between 4.0 and 5.5 m Potassium is usually administered orally, but when correction o arrhythmia is urgent and the serum potassium concentration is potassium may be administered cautiously by the intravenous r The electrocardiogram should be monitored for any evidence o sium toxicity (e.g., peaking of T waves) and to observe the effec the arrhythmia. Potassium salts may be dangerous in patients w manifest bradycardia or heart block due to digoxin (unless prim related to supraventricular tachycardia) and in the setting of ma digitalis overdosage (see Massive Digitalis Overdosage subsecti

Massive Digitalis Overdosage: Manifestations of life-threatenin city include ventricular tachycardia or ventricular fibrillation, or p gressive bradyarrhythmias, or heart block. The administration o than 10 mg of digoxin in a previously healthy adult, or more tha 4 mg in a previously healthy child, or a steady-state serum conc tion greater than 10 ng/mL often results in cardiac arrest.

DIGIBIND should be used to reverse the toxic effects of inges a massive overdose. The decision to administer DIGIBIND to a p who has ingested a massive dose of digoxin but who has not ye manifested life-threatening toxicity should depend on the likelihc that life-threatening toxicity will occur (see above).

Patients with massive digitalis ingestion should receive large of activated charcoal to prevent absorption and bind digoxin in t during enterocenteric recirculation. Emesis or gastric lavage may indicated especially if ingestion has occurred within 30 minutes patient's presentation at the hospital. Emesis should not be indu patients who are obtunded. If a patient presents more than 2 ho after ingestion or already has toxic manifestations, it may be un induce vomiting or attempt passage of a gastric tube, because s maneuvers may induce an acute vagal episode that can worsen talis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of pota from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the se of massive intoxication may be hazardous and should be avoide Hyperkalemia caused by massive digitalis toxicity is best treated DIGIBIND; initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSAGE AND ADMINISTRATION:

General: Recommended dosages of digoxin may require consid modification because of individual sensitivity of the patient to th drug, the presence of associated conditions, or the use of concu medications. In selecting a dose of digoxin, the following factors be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body weight.
2. The patient's renal function, preferably evaluated on the bas of estimated creatinine clearance.
3. The patient's age. Infants and children require different dos digoxin than adults. Also, advanced age may be indicative diminished renal function even in patients with normal seru creatinine concentration (i.e., below 1.5 mg/dL).
4. Concomitant disease states, concurrent medications, or oth factors likely to alter the pharmacokinetic or pharmacodyna profile of digoxin (see PRECAUTIONS).

Serum Digoxin Concentrations: In general, the dose of digoxin should be determined on clinical grounds. However, measureme serum digoxin concentrations can be helpful to the clinician in d mining the adequacy of digoxin therapy and in assigning certain abilities to the likelihood of digoxin intoxication. About two-third adults considered adequately digitalized (without evidence of tox have serum digoxin concentrations ranging from 0.8 to 2.0 ng/m However, digoxin may produce clinical benefits even at serum c trations below this range. About two-thirds of adult patients with cal toxicity have serum digoxin concentrations greater than 2.0 r However, since one-third of patients with clinical toxicity have co trations less than 2.0 ng/mL, values below 2.0 ng/mL do not rul the possibility that a certain sign or symptom is related to digoxi therapy. Rarely, there are patients who are unable to tolerate digo serum concentrations below 0.8 ng/mL. Consequently, the serur centration of digoxin should always be interpreted in the overall cal context, and an isolated measurement should not be used al the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between se and tissue, sampling of serum concentrations should be done ju

cal context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

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

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

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

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

1. If rapid digitalization 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 digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 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.

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

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

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

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

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

In a subset of approximately 1,800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in Table 5) the mean (±SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/mL and 0.97 ± 0.43 ng/mL, respectively.

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

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

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area)

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

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

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

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

† If no loading dose administered.

‡ 62.5 mcg = 0.0625 mg

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

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

† If no loading dose administered.

‡ 62.5 mcg = 0.0625 mg

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

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

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

Table 6: Daily Maintenance Doses in Children with Normal Renal Function

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

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

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

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

Dosage Adjustment When Changing Preparations: The difference in bioavailability between LANOXIN Injection or LANOXICAPS and LANOXIN Elixir Pediatric or LANOXIN Tablets must be considered when changing patients from one dosage form to another.

Doses of 100 mcg (0.1 mg) and 200 mcg (0.2 mg) of LANOXICAPS are approximately equivalent to 125-mcg (0.125-mg) and 250-mcg (0.25-mg) doses of LANOXIN Tablets and Elixir Pediatric, respectively (see table in CLINICAL PHARMACOLOGY: Pharmacokinetics).

HOW SUPPLIED:

LANOXIN (digoxin) Tablets, Scored 125 mcg (0.125 mg): Bottles of 100 with child-resistant cap (NDC 0173-0242-55) and 1000 (NDC 0173-0242-75); unit dose pack of 100 (NDC 0173-0242-56). Imprinted with LANOXIN and Y3B (yellow).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

LANOXIN (digoxin) Tablets, Scored 250 mcg (0.25 mg): Bottles of 100 with child-resistant cap (NDC 0173-0249-55), 1000 (NDC 0173-0249-75), and 5000 (NDC 0173-0249-80); carton of 12 bottles of 100 (NDC 0173-0249-01); unit dose pack of 100 (NDC 0173-0249-56). Imprinted with LANOXIN and X3A (white).

Store at 15° to 25°C (59° to 77°F) in a dry place.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

September 1997 RL-471

Amide
PHARMACEUTICAL, INC.

NDC 52152-145-06

DIGOXIN TABLETS, USP 125 mcg (0.125 mg)

Rx only

1000 TABLETS

Each Tablet Contains:
Digoxin, USP ..... 125 mcg (0.125 mg)

For indications, dosage, precautions, etc., see accompanying package insert.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 15°-25°C (59°-77°F) in a dry place and protect from light.

APPROVED

N 3 52152-145-05 5

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

DEC 2 3

Control No.:
Exp. Date:

7645-02

Amide
PHARMACEUTICAL, INC.

NDC 52152-145-06

DIGOXIN TABLETS, USP 125 mcg (0.125 mg)

Rx only

5000 TABLETS

Each Tablet Contains:
Digoxin, USP .... 125 mcg (0.125 mg)

For indications, dosage, precautions, etc., see accompanying package insert.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 15°-25°C (59°-77°F) in a dry place and protect from light.

N 3 52152-145-06 2

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

APPROVED

DEC 23

Control No.:
Exp. Date:
7645-02

Amide
PHARMACEUTICAL, INC.

NDC 52152-146-06

DIGOXIN TABLETS, USP

250 mcg (0.25 mg)

Rx only

5000 TABLETS

Each Tablet Contains:
Digoxin, USP .... 250 mcg (0.25 mg)

For indications, dosage, precautions, etc., see accompanying package insert.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 15°-25°C (59°-77°F) in a dry place and protect from light.

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
7649-02

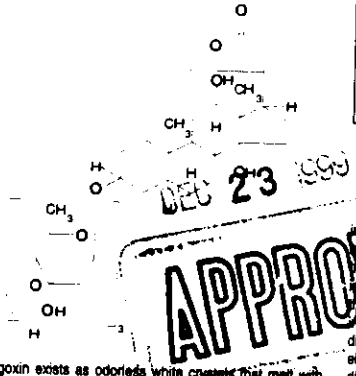
7652-06

DIGOXIN TABLETS, USP

Rx Only

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

Digoxin is described chemically as (3 β, 5 β, 12 β)-3-[(O-2, 6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-O-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D-ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$, its molecular weight is 780.96, and the structural formula shown:



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

Digoxin is supplied as 125-mcg (0.125-mg) or 250-mcg (0.25-mg) tablets for oral administration. Each tablet contains the labeled amount of digoxin USP and the following inactive ingredients: corn starch, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, lactose monohydrate and anhydrous lactose, silicon dioxide and stearic acid. In addition, the 0.125-mg tablet contains D&C Yellow No. 10 Aluminum Lake.

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

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

Table 1: Comparisons of the Systemic Availability and Equivalent Doses for Oral Preparations of Digoxin

Product	Absolute Bio-availability	Equivalent Doses(mcg)* Among Dosage Forms			
Digoxin Tablets	60-80%	62.5	125	250	500
Digoxin Pediatric Elixir	70-85%	62.5	125	250	500
Digoxin Solution in Capsules	90-100%	50	100	200	400
Digoxin Injection/IV	100%	50	100	200	400

*For example, 125-mcg Digoxin Tablets equivalent to 125 mcg Digoxin Pediatric Elixir equivalent to 100 mcg Digoxin Solution in Capsules equivalent to 100 mcg Digoxin Injection/IV.

In some patients, orally administered digoxin is converted to inactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggest that one in ten patients [illegible] tablets will degrade 40% or more of the [illegible] dose. As a result, certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. 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. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum 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: Serum Digoxin Concentrations).

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 best with lean (i.e., ideal) body weight, not total body weight.

Metabolism: Only a small percentage (16%) of a dose 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 be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion: Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to 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 and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5 to 2 days. 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 during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

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

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

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

Pharmacodynamic and Clinical Effects: The times to onset of pharmacologic effect and to peak effect of preparations of digoxin are shown in Table 2:

Table 2: Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of Digoxin

Product	Time to Onset of Effect*	Time to Peak Effect*
Digoxin Tablets	0.5-2 hours	2-6 hours
Digoxin Pediatric Elixir	0.5-2 hours	2-6 hours
Digoxin Solution in Capsules	0.5-2 hours	2-6 hours
Digoxin Injection/IV	5-30 minutes†	1-4 hours

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

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

INDICATIONS AND USAGE:

Atrial Fibrillation: Digoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS:

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

WARNINGS:

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 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.

Accessory AV Pathway (Wolff-Parkinson-White Syndrome): After intravenous digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting

accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

Use in Patients with Preserved Left Ventricular Systolic Function: Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS:

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). 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.

Use in Patients with Electrolyte Disorders: In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2 ng/mL, 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. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

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

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

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

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

Laboratory Test Monitoring: 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. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section.

Drug Interactions: Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result (see CLINICAL PHARMACOLOGY: Absorption). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine*, certain *anticancer drugs*, and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs [e.g., *quinine, penicillamine*] on serum digoxin concentration. *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 beta-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 advanced or complete heart block.

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

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

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 it's potential to affect fertility.

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 a pregnant woman or can affect reproductive capacity. Digoxin should be given to a pregnant woman only if clearly needed.

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

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

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).

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

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

Adults: ***Cardiac:*** Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of 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 multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

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

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

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

The following table summarizes the incidence of those adverse experiences listed above for patients treated with digoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients have been stable on digoxin, and were randomized to digoxin or placebo. The results shown in Table 3 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

Table 3: Adverse Experiences in Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)

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

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

OVERDOSAGE:

Treatment of Adverse Reactions Produced by Overdosage: Digoxin should be temporarily discontinued until the adverse reaction resolves. Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances or concurrent medications). Once the adverse reaction has resolved, therapy with digoxin may be reinstituted, following a careful reassessment of dose.

Withdrawal of digoxin may be all that is required to treat the adverse reaction. However, when the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed.

If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration should be given to the reversal of toxicity with DIGIBIND® [Digoxin Immune Fab (Ovine)] (see below), the use of atropine, or the insertion of a temporary cardiac pacemaker. However, asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac monitoring of the patient.

If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see below) or hypomagnesemia is present. DIGIBIND® [Digoxin Immune Fab (Ovine)] is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

Administration of Potassium: Every effort should be made to maintain the serum potassium concentration between 4 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium may be administered cautiously by intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. Potassium salts may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection).

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart block. The administration of more than 10 mg of digoxin in a previously healthy adult or more than 4 mg in a previously healthy child, or a steady-state serum concentration greater than 10 ng/mL often results in cardiac arrest.

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

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of potassium from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the setting of massive intoxication may be hazardous and should be avoided. Hyperkalemia caused by massive digitalis toxicity is best treated with DIGIBIND® [Digoxin Immune Fab (Ovine)]; initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSAGE AND ADMINISTRATION:

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

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

Serum Digoxin Concentrations: In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2 ng/mL. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2 ng/mL. However, since one third of patients with clinical toxicity have concentrations less than 2 ng/mL, values below 2 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 verses 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 hour after a dose.

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

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

Atrial Fibrillation: For the treatment of chronic atrial fibrillation, digoxin should be titrated to the minimum dose which achieves the desired ventricular rate control without causing excessive adverse effects. Data are not available to establish the appropriate targets for resting or exercise rates. Peak digoxin body stores larger than 8 to 12 mcg/kg are often required.

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

1. If rapid digitalization 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 digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 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.

Rapid Digitalization with a Loading Dose: Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 mcg/kg) (see PRECAUTIONS).

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

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

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

Digoxin Injection is frequently used to achieve rapid digitalization, with conversion to digoxin tablets or Digoxin Solution in Capsules for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see table, CLINICAL PHARMACOLOGY).

Maintenance Dosing: The doses of digoxin used in controlled trials have ranged from 125 to 500 mcg (0.125 to 0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 mcg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 mcg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 mcg (0.0625 mg) in patients

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with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.
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) x % Daily Loss/100
Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area.)

Table 4 provides average daily maintenance dose requirements of digoxin tablets based upon lean body weight and renal function:

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

Corrected Ccr	Lean Body Weight							Number of Days Before Steady State Achieved*
mL/min per 70 kg†	kg	50	60	70	90	90	100	
	lb	110	132	154	176	198	220	
0		62.5‡	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

*Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140-Age)/Scr. For women, this result should be multiplied by 0.85.
Note: This equation cannot be used for estimating creatinine clearance in infants or children.
†If no loading dose administered.
‡62.5 mcg = 0.0625 mg

Example: Based on the above table, a patient with an estimated lean body weight of 70 kg and a Ccr of 60 mL/min, should be given a dose of 250 mcg (0.25 mg) daily of digoxin tablets, usually taken after the morning meal. If no loading dose is administered, steady-state serum concentrations in this patient should be anticipated at approximately 11 days.
Infants and Children: In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area.
Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Daily maintenance doses for each age group are given in Table 5 and should provide therapeutic effects with minimum risk of toxicity in most patients. These recommendations assume the presence of normal renal function:

Table 5: Daily Maintenance Doses in Children with Normal Renal Function

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

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

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

Dosage Adjustment When Changing Preparations: The difference in bioavailability between Digoxin Injection or Digoxin Solution in Capsules and Digoxin Pediatric Elixir or digoxin tablets must be considered when changing patients from one dosage form to another.
Doses of 100 mcg (0.1 mg) and 200 mcg (0.2 mg) of Digoxin Solution in Capsules are approximately equivalent to 125-mcg (0.125- mg) and 250-mcg (0.25-mg) doses of digoxin tablets and Pediatric Elixir, respectively. (see table in CLINICAL PHARMACOLOGY: Pharmacokinetics).

HOW SUPPLIED:
Digoxin Tablets, USP 125 mcg (0.125 mg):
Yellow, round tablets, and imprinted with 'A 145' on the scored side of the tablet.
Available in bottles of 100s, 1000s and 5000s.

Digoxin Tablets, USP 250 mcg (0.25 mg):
White, round tablets, and imprinted with 'A 146' on the scored side of the tablet.
Available in bottles of 100s, 1000s and 5000s.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]
Dispense in a tight, light-resistant container as defined in the USP.

11/99

MANUFACTURED BY
AMIDE PHARMACEUTICAL, INC.,
101 East Main Street, Little Falls, NJ 07424 USA

Amide
PHARMACEUTICAL, INC.

NDC 52152-145-02

DIGOXIN TABLETS, USP
125 mcg (0.125 mg)

Rx only

100 TABLETS

Each Tablet Contains:
Digoxin, USP ..... 125 mcg (0.125 mg)
For indications, dosage, precautions, etc., see accompanying package insert.
Dispense in a tight, light-resistant container as defined in the USP.
Store at 15°-25°C (59°-77°F) in a dry place and protect from light.

APPROVED

N 3 52152-145-02 4

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.
Exp. Date: DEC 23

7644-02

Amide
PHARMACEUTICAL, INC.

NDC 52152-146-02

DIGOXIN TABLETS, USP
250 mcg (0.25 mg)

Rx only

100 TABLETS

Each Tablet Contains:
Digoxin, USP ..... 250 mcg (0.25 mg)
For indications, dosage, precautions, etc., see accompanying package insert.
Dispense in a tight, light-resistant container as defined in the USP.
Store at 15°-25°C (59°-77°F) in a dry place and protect from light.

APPROVED

N 3 52152-146-02 1

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.
Exp. Date: DEC 23 1999

7647-02

Amide
PHARMACEUTICAL, INC.

NDC 52152-146-05

DIGOXIN TABLETS, USP
250 mcg (0.25 mg)

Rx only

1000 TABLETS

Each Tablet Contains:
Digoxin, USP ..... 250 mcg (0.25 mg)
For indications, dosage, precautions, etc., see accompanying package insert.
Dispense in a tight, light-resistant container as defined in the USP.
Store at 15°-25°C (59°-77°F) in a dry place and protect from light.

APPROVED

N 3 52152-146-05 2

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

DEC 23

Control No.:
Exp. Date:

7648-02

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-282

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

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1. ~~CHEMIST'S REVIEW NO.~~ 4

2. ANDA# 40-282

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR ANDA SUBMISSION
The application is based on the reference listed drug Lanoxin® Tablets manufactured by Glaxo Wellcome (NDA 20-405). Amide had been marketing this product under the batch certification program (CFR 310.500), but received exemption from certification on 7/20/95. Amide then submitted an ANDA on 12/6/95, but the application was not accepted for filing since at that time there was no reference listed drug (RLD). On 9/30/97 FDA approved Glaxo Wellcome's NDA thus permitting OGD to accept a resubmission of Amide's ANDA (see review section #17 for further details).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Digoxin Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR
N/A

9. AMENDMENTS AND OTHER DATES
Firm:
Original Submission: 10/21/97
New Correspondence: 1/28/98
New Correspondence: 3/26/98
Major Amendment: 8/19/98
Minor Amendment: 4/12/99
Minor Amendment: 8/11/99
Minor Amendment: 11/12/99 (labeling)
Minor Amendment: 11/24/99 (labeling)

FDA:
Acceptance to File: 12/11/97
Major Deficiency Letter: 8/7/98
Minor Deficiency Letter: 3/30/99
Minor Deficiency Letter: 6/18/99

10. **PHARMACOLOGICAL CATEGORY**
Cardiotonic glycoside

11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**

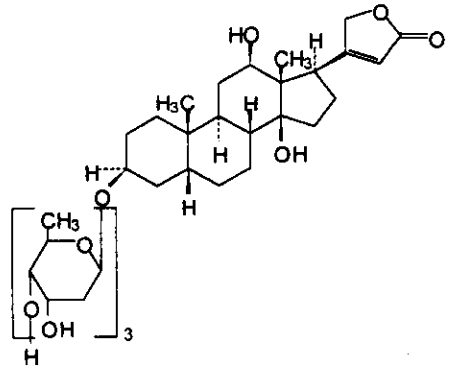
edient)

1

13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**
Tablets/Oral

14. **STRENGTH(s)**
0.125 mg & 0.25 mg

15. **CHEMICAL NAME AND STRUCTURE**



3ß-[(*O*-2,6-Dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl)oxy]-12ß,14-dihydroxy-5ß-card-20(22)-enolide.

CAS [20830-75-5]

$C_{41}H_{64}O_{14}$ 780.96

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
A draft federal register notice declared digoxin tablets to be a new drug and on 9/30/97 FDA approved Glaxo Wellcome's NDA for Lanoxin Tablets. Prior to this, digoxin tablets were considered a "grandfather drug" by the Agency and had been legally marketed without an approved application since 1936. The subject ANDA represents the first generic application accepted for digoxin tablets, although Amide and other firms are presently marketing the product under the batch certification program. When the federal register notice is finalized, all firms will have to have an approved application in order to market this product.

All CMC issues have been resolved with the 8/11/99 minor amendment. A labeling approval summary has been completed. The EER is acceptable, and the bio-study was found acceptable by the Division of Bioequivalence. It is to be noted that that portion of the ANDA relating to the 0.5 mg tablet was voluntarily withdrawn by Amide on 3/26/98, based on the fact that the innovator is no longer marketing Lanoxin 0.5 mg

18. **CONCLUSIONS/RECOMMENDATIONS**
Approval recommended

19. **REVIEWER** Susan Rosencrance

DATE COMPLETED
10/26/99; 11/29/99 (with amended labeling)

Page(s) 15

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

10/26/99.

Chemistry Review # 4

Page(s) _____

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Commercial/Confidential

Information and are not

releasable.

6/18/99

Chemistry Comments

#38

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

3/30/99

Chemistry Comment

#38

Page(s) 4

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

8/7/98

Chemistry Comments

#38

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-282

BIOEQUIVALENCE REVIEW(S)

JUL 18 1999

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 40-282 APPLICANT: Amide Pharmaceutical, Inc.

DRUG PRODUCT: Digoxin Tablets, USP, 0.125 mg and 0.25 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing as specified in USP 23 should be incorporated into your stability and quality control programs.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 40-282 APPLICANT: Amide Pharmaceutical, Inc.

DRUG PRODUCT: Digoxin Tablets, USP, 0.125 mg and 0.25 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing as specified in USP 23 should be incorporated into your stability and quality control programs.

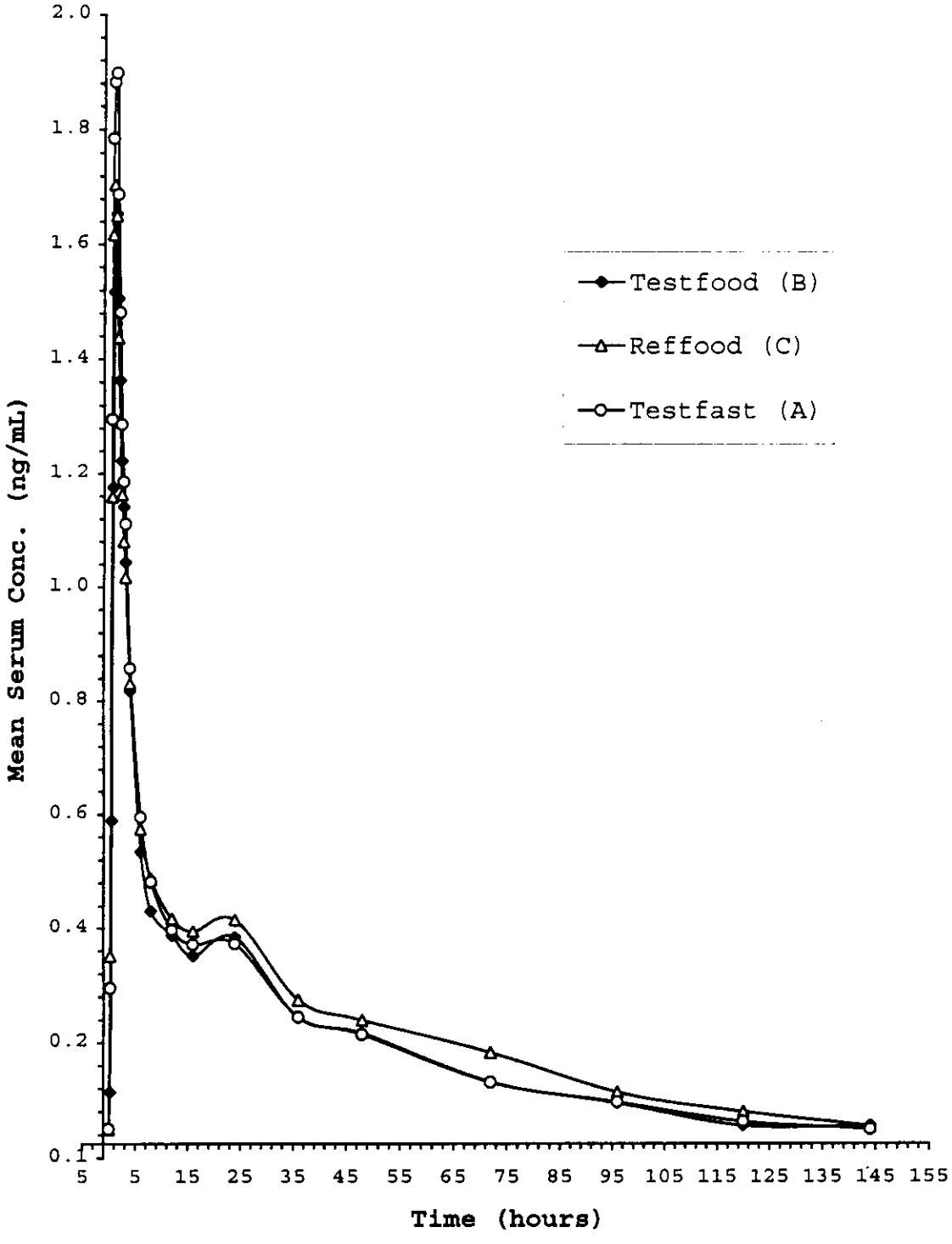
Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Fig. 1: Digoxin Tablet (2x0.25mg) Mean Serum Concentration-Time Plot; Food Study, n=19



ATTACHMENT I

AMIDE PHARMACEUTICAL, INC.

DIGOXIN TABLETS 0.125 mg

Comparative Product Profile for Digoxin 0.125 mg Tablets

PRODUCT	Digoxin Tablets 0.125 mg				Lanoxin Tablets 0.125 mg			
MFG. BY	Amide Pharmaceuticaal, Inc.				Glaxo Wellcome			
BATCH TYPE	Production				Brand			
MFG DATE	Sept 1998				N/A			
EXP.	Oct 2000				April 2001			
Batch #	8327A1				8E5189			
Assay	100.1				99.2			
Content	**Uniformity**							
1	98.6				103.7			
2	98.5				103.2			
3	98.6				103.1			
4	98.5				103.4			
5	100.8				99.4			
6	98.8				97.2			
7	98.9				98.1			
8	98.5				99.2			
9	98.9				98.7			
10	101.0				98.3			
Average	99.1				100.4			
RSD	1.0				2.6			
Dissolution								
Dissolution Conditions	Apparatus: I (Basket) Media: 500 mL, 0.1N HCl RPM: 120 Temp: 37C Sampling Time: 15, 30, 45 and 60 min. Limits:							
Time	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	80.8	87.6	92.8	99.1	73.6	83.5	89.3	98.0
St Dev.	2.3	1.4	1.3	2.2	2.0	1.4	0.8	2.6
RSD	2.8	1.6	1.4	2.2	2.8	1.6	0.9	2.7
High	85.7	89.6	94.5	101.6	77.8	86.2	90.7	103.5
Low	78.2	85.9	90.7	94.4	70.9	81.8	88.3	94.2

Digoxin Tablets, USP
0.125 and 0.250 mg
ANDA # 40-282
Reviewer: Chandra S. Chaurasia

Amide Pharmaceutical, Inc
Little Falls, NJ
Submission Date:
February 22, 1999
MARCH 18, 1999

Review of an Amendment: Bioequivalent Study and Dissolution Testing

I. Objective:

Review of Amide's amendment dated 02/22/99. The firm has submitted results of a food study and dissolution testing comparing its Digoxin Tablets, 0.25 mg strength, to Glaxo Wellcome's Lanoxin® Tablets, 0.25 mg strength. The firm has also requested for a biowaiver on the lower strength (0.125 mg) of the test drug digoxin.

II. Background

Amide had earlier submitted an acceptable *in vivo* bioequivalence study under fasting conditions comparing its digoxin 0.25 mg tablets to Glaxo Wellcome's Lanoxin® Tablets, 0.25 mg (submission date 10/21/97, review date 03/26/98, Reviewer Dr. Moo Park). However, the study was found incomplete due to the deficiencies mentioned below.

Deficiencies

1. Pharmacokinetic information in the PDR and the literature indicates that oral digoxin absorption is affected by food. A food study is recommended in addition to the current study under fasting conditions.

2. Only dissolution data at 15 minutes and 60 minutes were presented without a clear description of the dissolution method used. It is recommended that the firm describe the dissolution method used where the comparative dissolution data are being presented. Recommended sampling times are at 15, 30, 45 and 60 minutes to obtain a dissolution-time profile. Mean dissolution, range and %CV should be presented at each sampling point for the test and reference products in a tabular format.

For the 0.25 mg strength, the firm presented the dissolution data for Lot #4330A together with the reference data for comparison purposes instead of the data for the bio batch, Lot #4337A.

3. Assay and content uniformity for the reference product should be submitted.

4. The 0.5 mg strength of the reference product is a discontinued item according to the Orange Book (17th edition, supplement 11, 1997). A waiver request cannot be considered until a determination is made whether the 0.5 mg strength was withdrawn for safety or effectiveness reasons per 21 CFR 314.61. A citizen petition has to be submitted for the Agency to make a determination of withdrawal for other than safety or effectiveness reasons.

III. REVIEW OF FIRM'S RESPONSE:

III.1. RESPONSE TO DEFICIENCY #1

The firm has conducted a food study as recommended in the deficiency letter. Review of this study is summarized below.

Study Details

Protocol No. 983038: A Three-Way Crossover Randomized Study to Determine the Bioequivalence of Two Oral Digoxin Formulations in a Fed State and Limited Food Effects Compared to One Formulation in the Fasting State (2x0.25 mg Tablets)

A. Study Information

Clinical Site:

Principal Investigator:

Clinical Dates: n=21, Period 1: 10/21/98 to 10/23/98
n=21, Period 2: 11/18/98 to 11/20/98
n=21, Period 3: 12/16/98 to 12/18/98

Subjects: Entered - 21 normal healthy subjects (all males)
Completed - 19

Analytical Site:

Analysis Dates: 12/22/98 through 12/31/98

Storage Period: not more than 70 days at *-80 °C*

Study Design: Single-dose fed, three-way crossover

Washout Period: 28 days

Products Tested

Test Product: Digoxin tablets(0.25 mg)
Amide Pharmaceuticals, Inc.
*Lot #8287A2
Manufacturing Date 7/98
Expiration Date 7/00
Assay: 99.1%, Content Uniformity: 99.5%(RSD 0.7%)
Batch Size tablets
*(Please note the firm's bio batch used for the food study is different from the fasted studies since the batch used in the fasted study has expired).

Reference Product: Lanoxin® tablets (0.25 mg)
Glaxo Wellcome
Lot #8ZP0825, Expiration Date 4/00
Assay: 98.7%, Content Uniformity: 98.9% (RSD 0.4%)
Commercial Lot

Randomization: A=test, fasted
B=test, fed
C=reference, fed

CAB: 1,9,17,21
BCA: 2,3,6,11
CBA: 4,5,14
ABC: 7,8,10,19
ACB: 12,15,18
BAC: 13,16,20

Inclusion/Exclusion Criteria: Listed in Vol. 3.2, page 41. Subjects who participated in the study were in the age range of 26-45 years, and within 10% of their ideal

body weight as specified in the protocol.

Restrictions/Confinement: Listed in Vol. 3.2, page 42. The protocol also specified that subjects were not to take any medication including OTC products, for 14 days prior to the initial dose of medication, during the study, or during the washout period. Subjects abstained from xanthine- or caffeine-containing foods or beverages within 24 hours prior to the initial dosing and during the study. Subjects were confined from the evening before dosing until after the 36-hr blood draw. Subjects made return visit for the 48, 72, 96 120 and 144 hours blood draws.

Dosing: Subjects fasted overnight until 30 minutes prior to their scheduled dosing time, when they were given standard breakfast. Each oral dose (2x0.25 mg) was administered with 240 mL of water.

Blood Sampling: Five mL each, prior to dosing (time 0) and at 0.5,0.75,1,1.33,1.67,2,2.33,2.67,3,4,6,8,12,16, 24,36,48,72, 96,120 and 144 hours post-dose. Blood samples were allowed to clot at room temperature and then centrifuged under refrigeration. Separated serum samples were stored at -80°C pending analysis.

Analytical Method: , for serum digoxin. LOQ was 0.1 ng/mL.

Specificity: The firm has submitted specificity data of digoxin antibody from The (manufactured by ics, . It showed that the antibody is specific for digoxin and its methyl and acetyl derivatives, with an extremely low cross-reactivity to other naturally occurring steroids that may be present in patient samples. There is, however, an observed cross-reactivity of 50% with deslanoside and lanotoside C (Vol 3.6, pp 1227).

Linearity: Correlation coefficients of a 11 point standard curve(0.051 to 5.889 ng/mL) for digoxin ranged from 0.998 to 1.000 (Vol. 3.6, pp 1151,tab 3).

QC Samples: 0.257, 1.058 and 3.760 ng/mL

LOQ: 0.101 ng/mL (CV 5.7%)(Vol. 3.6 pp 1144&1149)

Accuracy Inter assay
QC samples: LQC 98.5%; MQC 104.7% and HQC 104.1%

Precision: Inter assay
QC samples: LQC 7.2%; MQC 3.1% and HQC 1.7%

Stability: The analytical analyses for the fast and food studies were conducted at the same site i.e., The firm's has previously submitted stability report as part of its pre-study assay validation for digoxin 0.25 mg tablets fasting bioequivalence study. The report was reviewed and found acceptable by the Agency (submission date 10/21/97, review date 03/26/98, Reviewer Dr. Moo Park). In particular, the long term stability of digoxin in human plasma and serum at -80 °C was found to be satisfactory for 513 and 112 days, respectively.

Missing Subject Values: In all, six samples corresponding to the following subjects were not received, and thus not considered valid for pharmacokinetic measures.

Subject	Period	Collection Time
3	2	48 hr
9	2	96 hr
11	3	120 and 144 hr
12	2	144 hr
21	3	36 hr

Comments: Analytical method is acceptable

B. Study Results

Clinical: Nineteen subjects out of a total of 21 enrolled completed the study.

Dropouts: Two subjects-subject #14 was withdrawn during Period 2 due to medical events and subject #16 was withdrawn before Period 2 due to a positive drug screen.

Adverse events: Subjects were monitored for medical events

throughout the study as specified in the protocol. Subject # 1,2,7,9,14 and 18 were examined by the Medical Advisor. No serious medical events were reported during the study. Summary of medical events are reported in Vol. 3.2, tables C3-C4, page 178-188.

Subject #14 experienced sore throat, head congestion, headache, coughing mucus, coughing, loose stool, dizziness and sweating. These events were mild in intensity and occurred between 2.7 hours prior to Period 2 dosing and 1.5 days after Period 2 dosing, and were judged remotely related or unrelated to the study drug. The subject was withdrawn from the study.

Protocol Deviations: None other than minor sampling deviations. Summarized in table C2, Vol. 3.2, pages 176-177.

Pharmacokinetic/Statistical Analysis: Pharmacokinetic Measures are given in tables 1 below (please also see Figure 1)

Table 1. Mean Serum Digoxin levels (ng/mL) and pharmacokinetic measures following an oral dose of 2x0.25 mg, digoxin tablet, fed conditions, n=19

Time (hr)	$Test_{food}$*	Ref_{food}*	$Test_{fast}$*	$(Test/Ref)_{food}$
0.0	0.000	0.000	0.000	0.00
0.25	0.064(250)	0.301(143)	0.245(151)	0.21
0.5	0.539(89)	1.109(78)	1.246(72)	0.49
0.75	1.125(69)	1.567(45)	1.735(41)	0.72
1.0	1.467(52)	1.655(29)	1.832(31)	0.89
1.33	1.603(31)	1.600(22)	1.848(27)	1.00
1.67	1.456(21)	1.387(18)	1.638(30)	1.05
2.0	1.313(19)	1.242(20)	1.431(30)	1.06
2.33	1.172(24)	1.113(18)	1.237(29)	1.05
2.67	1.091(26)	1.030(23)	1.135(30)	1.06
3.0	0.993(30)	0.967(24)	1.061(33)	1.03
4.0	0.767(27)	0.781(26)	0.808(19)	0.98
6.0	0.484(21)	0.524(21)	0.545(18)	0.92
8.0	0.381(20)	0.437(16)	0.432(18)	0.87
12.0	0.337(20)	0.367(18)	0.347(22)	0.92
16.0	0.301(19)	0.345(19)	0.321(21)	0.87
24.0	0.334(18)	0.365(31)	0.322(21)	0.92
36.0	0.194(24)	0.225(25)	0.195(32)	0.86
48.0	0.167(51)	0.190(7)	0.164(45)	0.88
72.0	0.082(92)	0.133(23)	0.081(90)	0.62

96.0	0.0451(35)	0.064(44)	0.047(131)	0.70
120.0	0.0064(36)	0.030(26)	0.013(291)	0.20
144.0	0.0064(36)	0.006(30)	0.000	1.00

*Data are arithmetic mean values (%CV)

PK Measures	Test	Reference	T/R[5]
AUC_t (ng*hr/mL)**	20.68±6.78	25.03±7.42	
AUC_i (ng*hr/mL)**	27.73±8.40	32.77±8.69	
C_{max} (ng/mL)**	1.88±0.48	1.93±0.48	
t_{max} (hr)	1.41±0.46	1.30±0.75	
$t_{1/2}$ (hr)	38.91±10.258	44.26±12.40	
Ln AUC_t	2.98±0.35	3.18±0.31	
Geometric mean	19.59	23.98	0.84
Ln AUC_i	3.28±0.32	3.46±.27	
Geometric mean	26.48	31.67	0.86
Ln C_{max}	0.60±0.25	0.63±0.26	
Geometric mean	1.82	1.87	0.98

**Data are arithmetic mean values (±S.D)
[5]ratio of LSMeans

Statistics on AUC_t/AUC_{inf} ratios for individual subjects:
Statistics on the AUCt/AUCinf ratios for individual subjects are summarized in Table 2 below.

Table 2. Statistics on AUC_t/AUC_{inf} Ratio

Treatment	Mean	Minimum	Maximum
$Test_{food}$ (n=19)	0.742±0.059	0.595	0.830
$Reference_{food}$ (n=19)	0.759±0.049	0.610	0.816
$Test_{fast}$ (n=18)	0.757±0.055	0.647	0.838

Comments:

1. The pharmacokinetic measures (AUC_t, AUC_i, and C_{max}) and ratio of their ln transformed means were recalculated by the reviewer. The reported values are in agreement with those obtained by the reviewer. There were no statistically significant period effects for any of these measures.
2. Ratios of means for AUC_t, AUC_i, and C_{max} between test non-fasting and reference non-fasting are within the acceptable limits of 80-125%.

C. **Formulations:** The formulations for test products are shown below:

Ingredients	Amount Per Tablet			
	0.25 mg		0.125 mg	
	% (w/w)	mg/tab	% (w/w)	mg/tab
Digoxin, USP	0.21	0.25	0.12	0.125
Total	100%	120.0	100%	105

III.2. RESPONSE TO DEFICIENCY #2

In response to Agency's request, the firm has conducted dissolution testing on its digoxin 0.125 and 0.25 mg tablets – from the batches used in the food study where applicable. The dissolution testing was conducted as per Agency's recommended sampling profiles i.e., at 15, 30, 45 and 60 minutes. Review of dissolution testing is summarized below.

Please note: as per firm's statement the dissolution profiles for the batches used in the fasted study could not be performed since the batches had expired.

DISSOLUTION TESTING: (USP Method, USP XXIII, p. 516)

Medium: 500 mL, 0.1N HCl at 37 °C
Apparatus: USP Apparatus 1(Basket), 120 rpm
Sampling Time: 15,30, 45 and 60 minutes
Tolerance: [The USP specified tolerances are for percentages dissolved, and are not to be interpreted as Q values.] Not less than of the labeled amount of digoxin is dissolved in 60 minutes for the average of 12 Tablets tested, and no individual Tablet has less than f the labeled amount of digoxin dissolved in 60 minutes. If the amount of digoxin dissolved in 60 minutes is more than for any individual

Tablet, the amount dissolved in 15 minutes is not more than for each individual Tablet.

(Note Firm's Proposed Tolerance: NLT minutes for 0.25 mg tablet, and NLT 0.125 mg tablet, please see Attachment I)

Number of tablets: 12

Results: See Table 3 below:

Table 3. *In Vitro* Dissolution Testing

Drug name: Digoxin Tablets
Dose strengths: 0.125 mg Lot #8327A1, Exp.10/00;
0.25 mg, Lot #8287A2, Exp. 07/00
RLD: Glaxo Wellcome's Lanoxin® Tablets
Dose Strengths: 0.125 mg, Exp.04/01
0.25 mg, Exp. 04/00
Method: USP 23 Apparatus 1 (Basket)
120 rpm, 0.1N HCl 500 mL at 37 °C
Proposed Specifications:

Results of dissolution testing for 0.25 mg digoxin tablets

Sampling time (min)	Test product Lot #8287A2, Exp. 07/00 Strength 0.25 mg			Reference product Lanoxin Lot #8ZP0825, Exp. 04/00 Strength 0.25 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	76.6%		1.7	75.1%		1.5
30	85.2%		2.4	84.3%		1.4
45	90.2%		2.0	90.6%		1.0
60	97.4%		0.8	98.2%		1.7

Results of dissolution testing for 0.125 mg digoxin tablets

Sampling time (min)	Test product Lot #8327A1, Exp. 10/00 Strength 0.125 mg			Reference product Lanoxin Lot #8E5189, Exp. 04/01 Strength 0.125 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	80.8%		2.8	73.6%		2.0
30	87.6%		1.6	83.5%		1.6
45	92.8%		1.4	89.3%		0.9
60	99.1%		2.2	98.0%		2.7

Comments:

1. The test and reference products used in the dissolution testing were from the same lots as used in the *in vivo* bioequivalence studies where applicable.
2. The formulation for the 0.125 mg strength is proportionally similar to the 0.25 mg strength that underwent bioequivalency testing.
3. The f_2 comparisons for test and reference products are summarized in Table 4 below.

Table 4. f_2 Comparisons of Test and Reference Products

Digoxin Tablets (Dose Strength)		f_2 Ratio
Test (0.125 mg)	Reference (0.125 mg)	66.7
Test (0.125 mg)	Test (0.25 mg)	75.8
Reference (0.125 mg)	Reference (0.25 mg)	91.7
Test (0.25 mg)	Reference (0.25 mg)	92.7

4. Firm's dissolution data is acceptable.

III.3. RESPONSE TO DEFICIENCY #3

As per Agency's request, the firm has submitted assay and content uniformity for the reference product (*please see on page 3 of this review under* ***Products Tested***).

Please Note: As per the firm's statement content uniformity for the reference product used for the fasted study was not tested initially, therefore the data are not included. Testing couldn't be done at this time since the batch has expired since December 1997.

III.4. RESPONSE TO DEFICIENCY #4

This deficiency was related to discontinuation of 0.5 mg strength of the reference listed drug product from the Orange Book (17th edition, supplement 11, 1997). The firm had withdrawn the portion of the ANDA applicable to Digoxin Tablets 0.5 mg.

Recommendations

1. The single-dose limited food bioequivalence study conducted by Amide Pharmaceuticals, Inc., on its Digoxin, 0.25 mg, tablets, Lot #8287A2, comparing it to Lanoxin® 0.25 mg tablets, Lot #8ZP0825 has been found acceptable by the Division of Bioequivalence. The firm has previously conducted an acceptable single-dose fasting bioequivalence study comparing its Digoxin, 0.25 mg tablets, Lot #4337A with innovator's Lanoxin 0.25 mg tablets, Lot # 4Y2215. These studies demonstrate that Amide's digoxin 0.25 mg, tablets are bioequivalent to the reference product Lanoxin®, 0.25 mg, tablets manufactured by Glaxo Wellcome.

2. The dissolution testing conducted by Amide Pharmaceutical, Inc. on its Digoxin, 0.25 mg, tablets, Lot #8287A2, is acceptable.

3. The dissolution testing conducted by Amide Pharmaceuticals on its digoxin 0.125 mg, tablet, lot #8327A1 is acceptable. The firm has conducted an acceptable in vivo bioequivalence fasting and food studies comparing its 0.25 mg tablet of test product with 0.25 mg tablets of the reference product Lanoxin® manufactured by Glaxo Wellcome. The formulation for the 0.125 mg strength is proportionally similar to the 0.25 mg strength that underwent bioequivalency testing. Waiver of *in vivo* bioequivalence study requirements for the 0.125 mg strength, Digoxin tablets is granted. The 0.125 mg tablets of Digoxin are therefore deemed bioequivalent to the 0.125 mg Lanoxin® tablets manufactured by Glaxo Wellcome.

4. The *in vitro* dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37 °C using USP Apparatus I (Basket) at 120 rpm. The test product should meet the following specifications:

for [illegible]

min [illegible]

/S/

Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 3/23/99

RD INITIALED YHUANG
FT INITIALED YHUANG /S/

Date: 3/23/99

Concur: _____

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: _____

31 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40-282 APPLICANT: Amide

DRUG PRODUCT: Digoxin Tablets, USP, o.125 mg, 0.25 mg and 0.5 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Pharmacokinetic information in the PDR and the literature indicates that oral digoxin absorption is affected by food. A food study is recommended in addition to the current study under fasting conditions.

2. Only dissolution data at 15 minutes and 60 minutes were presented without a clear description of the dissolution method used. The dissolution method used should be clearly described where the comparative dissolution data are being presented. Recommended sampling times are 15, 30, 45 and 60 minutes to obtain a dissolution-time profile. It is recommended that mean dissolution, range and %CV be presented at each sampling point for the test and reference products in a tabular format.

   For the 0.25 mg strength, you presented the dissolution data for Lot #4330A together with the reference data for comparison purposes instead of the data for the bio batch, Lot #4337A.

3. Submission of assay and content uniformity for the reference product is advised.

4. The 0.5 mg strength of the reference listed drug product is a discontinued item according to the Orange Book (17th edition, supplement 11, 1997). A waiver request for this strength cannot be considered until a determination is made whether the 0.5 mg strength was withdrawn for safety or effectiveness reasons per 21 CFR 314.61. A citizen petition has to be submitted for the Agency to make a determination of withdrawal for other than safety or effectiveness reasons. However, *in vivo* bioequivalence studies may be needed for the approval of the 0.5 mg strength.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Digoxin Tablets	Amide Pharmaceutical
0.125 mg, 0.25 mg and 0.5 mg	Little Falls, NJ
ANDA #40-282	Submission Date: 10/21/1997
Reviewer: Moo Park	
Filename: 40282sdw.o97	

Review of an In Vivo Bioequivalence Study, Dissolution Data and Waiver Requests

I. Objective

Review of Amide's in vivo bioequivalence study under fasting conditions comparing its Digoxin Tablets, 0.25 mg strength, to Glaxo Wellcome's Lanoxin[R] Tablets, 0.25 mg strength. Dissolution data and waiver requests for 0.125 mg and 0.5 mg strengths were submitted for review.

II. Background

Digoxin is one of the cardiac glycosides, extracted from the leaves of Digitalis lanata. Digoxin is practically insoluble in water and in ether; slightly soluble in diluted alcohol and in chloroform; and freely soluble in pyridine.

GI absorption of digoxin is a passive process. Glaxo Wellcome's Lanoxin[R] Tablets have shown absolute bioavailability of 60-80%. When digoxin tablets are taken after meals, the rate of absorption slows down, but the total amount of digoxin absorbed does not change. Following drug administration, a 6 to 8 hour distribution phase is observed. This is followed by a much more gradual serum concentration decline. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, that with chronic use, the steady-state post-distribution serum levels are in equilibrium with tissue levels and correlate with pharmacologic effects. Elimination of digoxin follows first-order kinetics. Following intravenous administration to normal subjects, 50% to

70% of a digoxin dose is excreted unchanged in the urine. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2 days.

III. Study Details

Protocol No.	950048
Applicant	Amide Pharmaceutical, Little Falls, NJ
Study sites	
Investigators	
Study dates	Period 1: 7/6/95-7/14/95 Period 2: 8/17/95-8/25/95
Study design	Open-label, randomized, 2-way crossover study under fasting conditions.
Subjects	Of the 26 healthy, adult male volunteers enrolled in the study, three subjects did not complete the crossover study. Subject #1 was withdrawn from the Period 2 due to the criteria for heart rate. Subjects # 15 and 22 elected to withdraw from the Period 2 study.
Drug products	Treatment 1 (test product): Amide's Digoxin Tablets, 0.25 mg strength, Lot #4337A3. Treatment 2(reference product): Glaxo Wellcome's Lanoxin^{R} Tablets, 0.25 mg strength, Lot #4Y2215; Expiry date: 12/97.
Dosing	Single oral dose of 0.5 mg (=2 x 0.25 mg tablets) digoxin with 240 mL water.
Food and fluid	Subjects were required to fast overnight before dosing and for 4 hours thereafter. Water was not permitted for 2 hours before and 4 hours after the dose, but were allowed at all other times. Standard meals were provided at 4 and 9 hours after drug administration and at appropriate times thereafter.

Housing	Subjects were housed in the clinical facility from 12 hours before dosing until after the 36-hour blood draw.
Washout	Six weeks between doses.
Blood samples	Blood samples (1 x 5 mL each) were collected in Vacutainers containing EDTA at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours after dosing. Blood samples were allowed to clot at room temperature and then centrifuged under refrigeration. Separated serum samples were stored at -80°C pending analysis.
IRB	Institutional Review Board
Informed consent	Each subject read and signed the Informed Consent form.
Assay method for blood samples	digoxin. LOQ was 0.1 ng/mL.
Analytes	Digoxin in serum.
PK analysis	AUCT, AUCI, CMAX, TMAX, KE, and THALF were calculated from the serum digoxin levels.
Statistical analysis	90% confidence intervals for log-transformed AUCT, AUCI and CMAX were calculated.

IV. Assay Method Validation

A procedure was used to determine serum digoxin levels. A commercially available kit, from Diagnostics, was used in the assay.

The pre-study assay validation was conducted in sodium heparin human plasma as the matrix. In order to apply the method in human serum, method cross-validation was performed to demonstrate that the assay performance in human serum was comparable to that in sodium heparin plasma.

A. Pre-study validation

1. Specificity: The firm submitted specificity data of digoxin antibody from It showed that the antibody is specific for digoxin and its methyl and acetyl derivatives, with an extremely low cross-reactivity to other naturally occurring steroids that may be present in patient samples. There is, however, an observed cross-reactivity of 50% with deslanoside and lanotoside C.

2. Sensitivity: The lower limit of quantitation was 0.1 ng/mL.

3. Linearity: Data reduction of the output from the gamma counter was performed by the method. For linearizing the standard curve, the response variable (bound radioactivity) was Logit-transformed. The immunoassay dose-response curve is described by y=a + b logx, where y is the transformed response variable, x is the concentration and a and b are constants. Standard curves for digoxin concentrations ranging from 0.1 ng/mL to 4.84 ng/mL showed mean correlation coefficient of 0.9998.

4. Precision and accuracy: Precision and accuracy data for quality control samples (digoxin in human plasma) are shown in Table IV-1. The data are acceptable.

Table IV-1. Precision and Accuracy for QC Samples
Digoxin in Sodium Heparin Human Plasma

Matrix	Conc, ng/mL	Type	#Assay	n	Precision Range of %CV	Accuracy Mean %Input
Human plasma	0.1	Intra-assay	5	5	3.5-12.1	103
Human plasma	0.25	Intra-assay	5	5	2.1-5.2	99.2
Human plasma	1.01	Intra-assay	5	5	0.5-3.0	101
Human plasma	3.63	Intra-assay	5	5	1.1-5.1	101

Human plasma	5.376	Intra-assay	2	10	1.6-2.6	101
Human serum	0.101	Intra-assay	3	10	3.6-6.3	98.9
Human serum	0.252	Intra-assay	1	10	4.6	85.6
Human serum	1.008	Intra-assay	1	10	2.6	106
Human serum	3.584	Intra-assay	1	10	2.5	103
Human serum	5.376	Intra-assay	1	10	2.2	98.7

5. Stability: Stability data are summarized in Table IV-2. The data are acceptable.

Table IV-2. Stability Data
Digoxin

Sample	Conc, ng/mL	Storage condition	n	%Initial	%CV
Digoxin in human plasma	0.25	6 hrs @RT	10	98.5	2.5
Digoxin in human plasma	3.63	6 hrs @RT	10	101	1.5
Digoxin in human plasma	0.25	3 freeze-thaw cycles	10	93.7	6.8
Digoxin in human plasma	3.63	3 freeze-thaw cycles	10	98.1	1.7
Digoxin in human plasma	0.25	513 days @-80°C	10	96.5	5.4
Digoxin in human plasma	3.63	513 days @-80°C	10	102	1.9

Digoxin in human plasma	0.25	35 days @-20°C	10	101	3.1
Digoxin in human plasma	3.63	35 days @-20°C	10	104	1.8
Digoxin in human serum	0.252	11.5 hrs @RT	10	97.6	2.2
Digoxin in human serum	3.584	11.5 hrs @RT	10	99.7	1.9
Digoxin in human serum	0.252	3 freeze-thaw cycles	10	101	4.1
Digoxin in human serum	3.584	3 freeze-thaw cycles	10	104	2.5
Digoxin in human serum	0.252	112 days @-80°C	10	98.0	7.2
Digoxin in human serum	3.584	112 days @-80°C	10	106	2.9

V. *In Vivo* Results with PK and Statistical Analyses

Of the 26 healthy adult male volunteers, three subjects did not complete the crossover. Subject #1 was withdrawn from the Period 2 due to the criteria for heart rate. Subjects # 15 and 22 elected to withdraw from the Period 2 study. This reviewer disqualified the Subject #23 due to the vomiting at 2.4 hours after the dosing. Therefore, data for the 22 subjects were used in the PK and statistical analyses. The firm reported the results based on the study analyses on 23 subjects including Subject #23.

Protocol deviation: The protocol specified 28 subjects. However, only 26 volunteers were enrolled due to unexpected dropouts. There were relatively minor deviations in sampling times and food and beverage consumptions. The firm concluded that the deviations reported were unlikely to affect the bioavailability comparison.

Medical events: Nine subjects reported 28 events under the test

product and 7 subjects reported 18 events under the reference products. Under the test product, Subject #17 began to vomit at 1.5 days after the dosing and Subject #23 vomited at 2.4 hours after the dosing. Most of the events were mild.

Mean serum digoxin levels: The mean serum digoxin-time profiles for the test and reference products were comparable as shown in Table V-A-1 and Fig P-1. The peak mean serum digoxin levels for the test and reference products were 1.89 ng/mL and 1.75 ng/mL, both occurring at 1 hour.

TABLE V-A-1. MEAN SERUM DIGOXIN LEVELS FOR TEST AND REFERENCE PRODUCTS UNDER FASTING CONDITIONS
UNIT: SERUM LEVEL=NG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION
Test Lot #4337A3; Ref Lot #4Y2215

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.28	0.31	0.25	0.37	1.14
0.5	1.16	0.71	1.13	0.56	1.03
0.75	1.71	0.53	1.62	0.44	1.06
1	1.89	0.44	1.75	0.34	1.08
1.25	1.85	0.45	1.69	0.37	1.10
1.5	1.73	0.41	1.58	0.34	1.10
2	1.45	0.31	1.39	0.40	1.04
3	1.11	0.28	1.14	0.27	0.98
4	0.94	0.27	0.95	0.24	0.98
6	0.64	0.14	0.64	0.13	1.00
8	0.47	0.11	0.46	0.07	1.03
12	0.37	0.08	0.36	0.08	1.01
16	0.35	0.07	0.33	0.06	1.04
24	0.35	0.09	0.36	0.07	0.99
36	0.22	0.05	0.22	0.05	0.99
48	0.21	0.04	0.21	0.05	0.98
72	0.14	0.06	0.13	0.06	1.03
96	0.07	0.07	0.07	0.07	1.00
120	0.04	0.05	0.04	0.06	0.89
144	0.00	0.00	0.02	0.04	0.00
168	0.00	0.00	0.00	0.00	.
192	0.00	0.00	0.00	0.00	.

PK parameters and 90% confidence intervals: Arithmetic and geometric means for the pharmacokinetic parameters for the test and reference products were summarized in Table V-A-2. The 90% confidence intervals and the test/reference ratios for the log-transformed least-squares means for AUCT, AUCI and CMAX were summarized in Table V-A-3. The 90% confidence intervals for the

log-transformed AUCT, AUCI and CMAX were all within 80-125% range.

Sequence effect was found significant with the log-transformed AUCT and AUCI.

TABLE V-A-2. ARITHMETIC/GEOMETRIC MEANS AND TEST/REF RATIOS FOR DIGOXIN UNDER FASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	36.05	8.88	36.55	10.12	0.99
AUCT	26.48	6.76	26.81	7.43	0.99
CMAX	2.10	0.42	1.93	0.32	1.09
KE	0.01	0.00	0.01	0.01	1.01
LAUCI	34.90	0.27	35.25	0.28	0.99
LAUCT	25.58	0.28	25.83	0.28	0.99
LCMAX	2.06	0.20	1.90	0.16	1.08
THALF	51.82	15.27	55.54	20.62	0.93
TMAX	1.18	0.69	1.38	0.89	0.86

TABLE V-A-3. LSMEANS AND 90% CONFIDENCE INTERVALS FOR DIGOXIN UNDER FASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LSM1=TEST; LSM2=REFERENCE; RLSM12=LSM1/LSM2 RATIO
LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	35.48	36.29	0.98	89.20	106.35
AUCT	26.43	26.62	0.99	90.87	107.67
CMAX	2.09	1.93	1.08	100.77	115.79
LAUCI	34.29	34.99	0.98	89.57	107.20
LAUCT	25.58	25.64	1.00	91.54	108.73
LCMAX	2.05	1.91	1.07	99.79	115.65

Statistics on test/reference ratios for individual subjects:
Statistics on the test/reference ratios for individual subjects were summarized in Table V-A-4.

TABLE V-A-4. STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	22	1.02	0.23	0.63	1.55
RAUCI12	20	1.00	0.24	0.63	1.59
RCMAX12	22	1.10	0.21	0.71	1.46
RTMAX12	22	1.07	0.55	0.17	2.00
RKE12	20	1.17	0.59	0.63	3.17
RTHALF12	20	0.99	0.34	0.31	1.60

Statistics on AUCT/AUCI ratios for individual subjects:
Statistics on the AUCT/AUCI ratios for individual subjects were summarized in Table V-A-5.

TABLE V-A-5. STATISTICS ON AUCT/AUCI RATIOS

Analysis Variable : AUCRATIO

TRT=1

N	Mean	Std Dev	Minimum	Maximum
20	0.75	0.03	0.68	0.80

TRT=2

N	Mean	Std Dev	Minimum	Maximum
22	0.74	0.06	0.61	0.83

VI. Product Information

1. Formulation

Test formulations for the 0.125 mg, 0.25 mg, and 0.5 mg strengths are shown in Table VI-1.

Table VI-1. Test Formulations

Ingredient	0.125 mg	0.25 mg	0.5 mg
Digoxin, USP	0.1275	0.255	0.515
sll package insert			
D&C Yellow			
Total weight	105	120	130

2. Assay and content uniformity

Table VI-2 summarizes the assay and content uniformity for the test and reference products. Data for the reference product were not submitted.

Table VI-2. Assay and Content Uniformity

Product	Assay, %	Content Uniformity, % (%CV)
Amide's Digoxin Tablets 0.25 mg; Lot #4337A		
Glaxo Wellcome's Lanoxin® Tablets, 0.25 mg; Lot #4Y2215; Expiry date: 12/97		

VII. Dissolution

Only dissolution data at 15 minutes and 60 minutes were submitted without clear description of dissolution method used as shown in Table VII-1. The dissolution data submitted are not satisfactory even though the mean dissolution at 60 minutes for the test and reference products meet the USP specifications. The firm should describe the dissolution method clearly where the comparative dissolution data are being presented. Sampling should be done at 15, 30, 45 and 60 minutes to obtain a dissolution-time profile. Mean dissolution, range and %CV should be presented at each sampling point for the test and reference products in a tabular format.

VIII. Comments

1. **Two-way crossover study under fasting conditions**: Of the 26 healthy adult male volunteers, three subjects did not complete the crossover. Subject #23 was removed from the data analyses due to vomiting at 2.4 hours after dosing. Twenty-two subjects were used in the data analyses. The mean serum digoxin-time profiles for the test and reference products were comparable. The 90% confidence intervals for log-transformed AUCT, AUCI and CMAX were all within the 80-125% range.

2. **Post prandial study**: Pharmacokinetic information in the PDR and the literature indicates that digoxin absorption is affected by food. A food study should be performed in addition to the study under fasting conditions.

3. Assay method validation for the serum samples is acceptable.

4. Only dissolution data at 15 minutes and 60 minutes were summarized without a clear description of the dissolution method used. The dissolution data submitted are not satisfactory even though the mean dissolution at 60 minutes for the test and reference products meet the USP specifications. The firm should describe the dissolution method clearly where the dissolution data are being presented. Sampling should be done at 15, 30, 45 and 60 minutes to obtain a dissolution-time profile. Mean dissolution, range and %CV should be presented at each

sampling point for the test and reference products in a tabular format.

5. Nine subjects reported 28 events under the test product and 7 subjects reported 18 events under the reference product. Under the test product, Subject #17 began to vomit at 1.5 days after the dosing and Subject #23 vomited at 2.4 hours after the dosing. Most of the events were mild.

6. Assay and content uniformity for the test product were acceptable. Assay and content uniformity for the reference product should be submitted.

7. The batch size of the bio-batch (4337A): tablets.

8. The 0.5 mg strength of the reference product is a discontinued item according to the Orange Book (17th edition, supplement 11, 1997). Glaxo Welcome's withdrawal of 4 strengths (0.0625 mg, 0.1875 mg, 0.375 mg and 0.5 mg tablets) was dated 9/30/97. A waiver request cannot be considered until a determination is made whether the 0.5 mg strength was withdrawn for safety or effectiveness reasons per 21 CFR 314.61. A citizen petition has to be submitted for the Agency to make a determination of withdrawal for other than safety or effectiveness reasons.

IX. Deficiencies

1. Pharmacokinetic information in the PDR and the literature indicates that oral digoxin absorption is affected by food. A food study is recommended in addition to the current study under fasting conditions.

2. Only dissolution data at 15 minutes and 60 minutes were presented without a clear description of the dissolution method used. It is recommended that the firm describe the dissolution method used where the comparative dissolution data are being presented. Recommended sampling times are at 15, 30, 45 and 60 minutes to obtain a dissolution-time profile. Mean dissolution, range and %CV should be presented at each sampling point for the test and reference products in a tabular format.

For the 0.25 mg strength, the firm presented the dissolution data for Lot #4330A together with the reference data for comparison purposes instead of the data for the bio batch, Lot #4337A.

3. Assay and content uniformity for the reference product should be submitted.

4. The 0.5 mg strength of the reference product is a discontinued item according to the Orange Book (17th edition, supplement 11, 1997). A waiver request cannot be considered until a determination is made whether the 0.5 mg strength was withdrawn for safety or effectiveness reasons per 21 CFR 314.61. A citizen petition has to be submitted for the Agency to make a determination of withdrawal for other than safety or effectiveness reasons.

X. Recommendation

The *in vivo* bioequivalence study under fasting conditions conducted by Amide on its Digoxin Tablets, 0.25 mg strength, lot #4337A, comparing it to Glaxo Wellcome's Lanoxin^{R} Tablets, 0.25 mg; Lot #4Y2215, has been found incomplete. The firm should respond to the deficiencies #1-4.

The firm should be informed of the recommendation and deficiencies #1-4.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED MMAKARY
FT INITIALED MMAKARY /S/

Concur: /S/ Date: 3/26/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

File history: Draft (2/26/98); Revised (3/25/98); Final (3/25/98)

Table VII-1. *In Vitro* Dissolution Testing Data	
I. General Information	
Drug Product (Generic Name)	Digoxin Tablets
Strength	0.125 mg, 0.25 mg, and 0.5 mg tablets
ANDA Number	40-282
Applicant	Amide
Reference Drug Product	Glaxo Wellcome's Lanoxin[R] Tablets, 0.125 mg, 0.25 mg, and 0.5 mg strengths.
II. USP Method for Dissolution Testing	
Medium and Volume	0.1 N HCl; 500 mL
Apparatus and rpm	I; 120 rpm
Time	60 min
Tolerances	
Assay Method	

III. Dissolution Data (%)

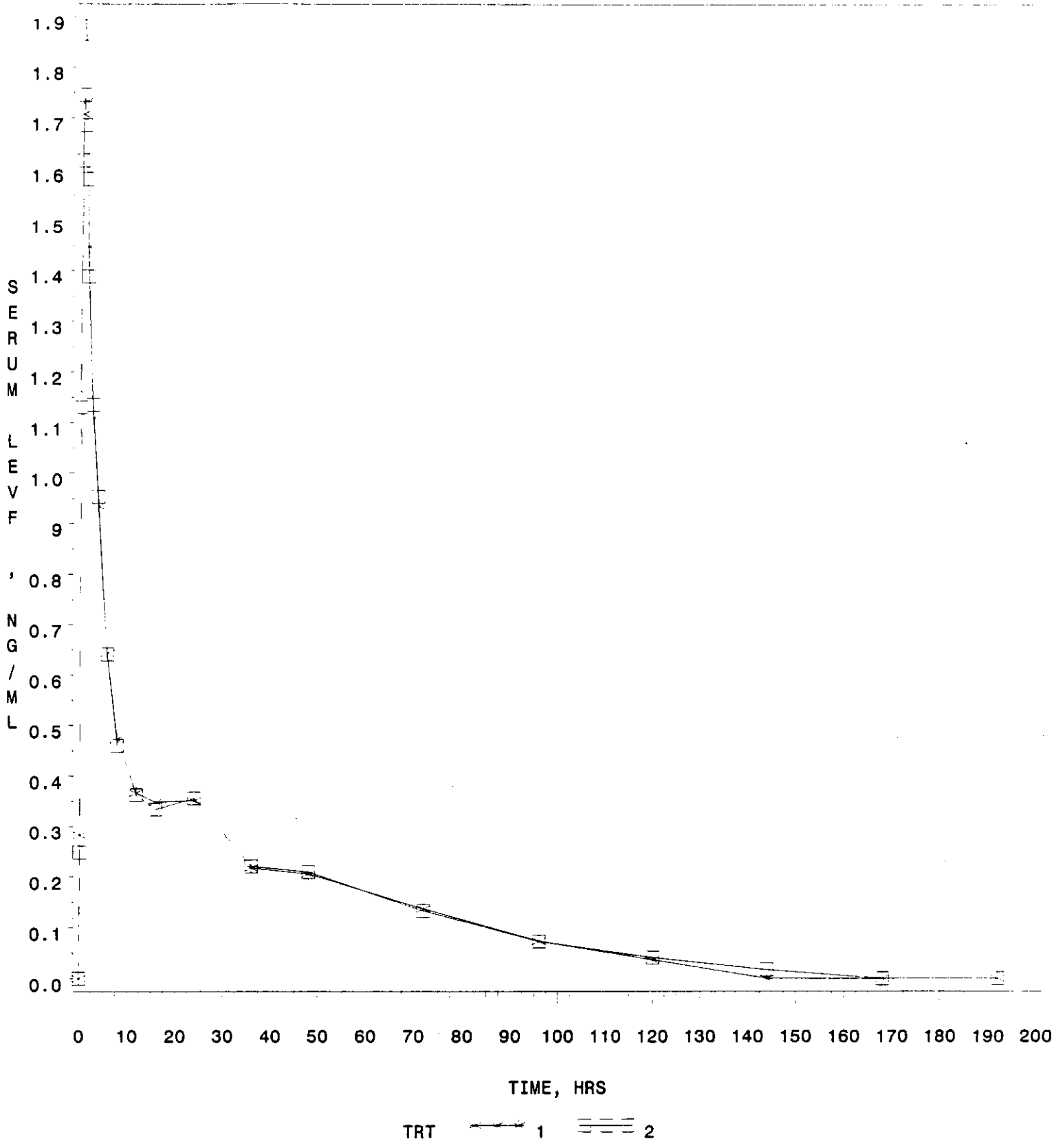
Time	Test Product Lot No: 4318A Strength: 0.125 mg No of Units: 12			Reference Product Lot No: 3N1311 Strength: 0.125 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	83.7			51.0		
60	98.9			72.9		

Time	Test Product Lot No: 4337A Strength: 0.25 mg No of Units: 12			Reference Product Lot No: 4Y2215 Strength: 0.25 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	73.9			67.8		

60	92.2			89.7		
Time	Test Product Lot No: 4296A Strength: 0.5 mg No of Units: 12			Reference Product Lot No: 2R1816 Strength: 0.5 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	80.8			57.9		
60	93.4			80.8		

FIG P-/. SERUM DIGOXIN LEVELS

DIGOXIN TABLETS, 0.25 MG, ANDA #40-282
UNDER FASTING CONDITIONS
DOSE=2 X 0.25 MG



1=TEST(AMIDE) 2=REF(GLAXO-WELLCOME)

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40-282 APPLICANT: Amide

DRUG PRODUCT: Digoxin Tablets, USP, o.125 mg, 0.25 mg and 0.5 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Pharmacokinetic information in the PDR and the literature indicates that oral digoxin absorption is affected by food. A food study is recommended in addition to the current study under fasting conditions.

2. Only dissolution data at 15 minutes and 60 minutes were presented without a clear description of the dissolution method used. The dissolution method used should be clearly described where the comparative dissolution data are being presented. Recommended sampling times are 15, 30, 45 and 60 minutes to obtain a dissolution-time profile. It is recommended that mean dissolution, range and %CV be presented at each sampling point for the test and reference products in a tabular format.

   For the 0.25 mg strength, you presented the dissolution data for Lot #4330A together with the reference data for comparison purposes instead of the data for the bio batch, Lot #4337A.

3. Submission of assay and content uniformity for the reference product is advised.

4. The 0.5 mg strength of the reference listed drug product is a discontinued item according to the Orange Book (17th edition, supplement 11, 1997). A waiver request for this strength cannot be considered until a determination is made whether the 0.5 mg strength was withdrawn for safety or effectiveness reasons per 21 CFR 314.61. A citizen petition has to be submitted for the Agency to make a determination of withdrawal for other than safety or effectiveness reasons. However, *in vivo* bioequivalence studies may be needed for the approval of the 0.5 mg strength.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-282

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

18 1999

ANDA Number: **40-282** Date of Submission: **April 12, 1999**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Digoxin Tablets USP, 0.125 mg and 0.25 mg**

Labeling Deficiencies:

INSERT

1. CLINICAL PHARMACOLOGY

   Delete the "Chronic Heart Failure" subsection.

2. DOSAGE AND ADMINISTRATION

   a. Retain the "General" and "Serial Digoxin Concentrations" subsections.

   b. Atrial Fibrillation

      Revise to read - For the treatment of chronic atrial fibrillation, digoxin should be titrated to the minimum dose which achieves the desired ventricular rate control without causing excessive adverse effects. Data are not available to establish the appropriate targets for resting or exercise rates. Peak digoxin body stores larger than 8 to 12 mcg/kg are often required.

   c. With regard to the mock up of the innovator insert labeling - insert the bracketed text (minus) the lined out text immediately following the above paragraph in the Atrial Fibrillation subsection.

Please revise your insert labeling, as instructed above, and submit final print (or draft, if you prefer) insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Innovator insert labeling mock-up

V 4-UP FOR WHAT TO CHRVE OUT OF THE HEART FAILURE, ADULTS SUBSECTION TO PRESERVE THE EXCLUSIVITY

of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

OVERDOSAGE:

Treatment of Adverse Reactions Produced by Overdosage: Digoxin should be temporarily discontinued until the adverse reaction resolves. Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances or concurrent medications). Once the adverse reaction has resolved, therapy with digoxin may be reinstituted, following a careful reassessment of dose.

Withdrawal of digoxin may be all that is required to treat the adverse reaction. However, when the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed.

If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration should be given to the reversal of toxicity with DIGIBIND® (Digoxin Immune Fab (Ovine)) (see below), the use of atropine, or the insertion of a temporary cardiac pacemaker. However, asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac monitoring of the patient.

If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see below) or hypomagnesemia is present. DIGIBIND is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

Administration of Potassium: Every effort should be made to maintain the serum potassium concentration between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium may be administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. Potassium salts may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection).

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart block. The administration of more than 10 mg of digoxin in a previously healthy adult, or more than 4 mg in a previously healthy child, or a steady-state serum concentration greater than 10 ng/mL often results in cardiac arrest.

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

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enterocentric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of potassium from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the setting of massive intoxication may be hazardous and should be avoided. Hyperkalemia caused by massive digitalis toxicity is best treated with DIGIBIND; rarely treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSAGE AND ADMINISTRATION:

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

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

Serum Digoxin Concentrations: In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clini-

heart block, consideration should be given to the administration of digoxin with DIGIBIND® [Digoxin Immune Fab (Ovine)] (see below), the use of atropine, or the insertion of a temporary cardiac pacemaker. However, asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac monitoring of the patient.

If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see below) or hypomagnesemia is present. DIGIBIND is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

Administration of Potassium: Every effort should be made to maintain the serum potassium concentration between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium may be administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. Potassium salts may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection).

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart block. The administration of more than 10 mg of digoxin in a previously healthy adult, or more than 4 mg in a previously healthy child, or a steady-state serum concentration greater than 10 ng/mL often results in cardiac arrest.

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

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enterohepatic recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of potassium from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the setting of massive intoxication may be hazardous and should be avoided. Hyperkalemia caused by massive digitalis toxicity is best treated with DIGIBIND; initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSAGE AND ADMINISTRATION:

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

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

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

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just

Place bracketed text and tables under the "Atrial Fibrillation" subsection after the first paragraph (see labeling review).

~~a brief~~ adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 5 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

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

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

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

1. If rapid digitalization 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 digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 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.

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

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, with careful assessment of clinical response before each additional dose. If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

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

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

Maintenance Dosing: The doses of digoxin used in controlled trials ~~in patients with heart failure~~ have ranged from 125 to 500 mcg (0.125 to 0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 mcg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 mcg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 mcg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response. ~~In a subset of approximately 1,300 patients enrolled in the DIG trial (veraison dosing was based on an algorithm similar to that in Table 5) the mean (±SD) serum digoxin concentrations at 1 month and 12 months were 1.21 ± 0.47 ng/mL and 0.97 ± 0.42 ng/mL, respectively.~~

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

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

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area)

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

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

Corrected Ccr (mL/min per 70 kg)[1]	Lean Body Weight						Number of Days Before Steady State Achieved[2]
	kg 50	60	70	80	90	100	
	lb 110	132	154	176	198	220	
0	62.5[3]	125	125	125	187.5	187.5	22
10	125	125	125	187.5	187.5	187.5	19
20							

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

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, with careful assessment of clinical response before each additional dose. If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

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

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

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

In a subset of approximately 1,300 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in Table 5) the mean (±SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/mL and 0.97 ± 0.43 ng/mL, respectively.

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

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

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area)

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

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

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

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

† If no loading dose administered.

‡ 62.5 mcg = 0.0625 mg

Corrected Ccr (mL/min per 70 kg)*	kg / lb	50 / 110	60 / 132	70 / 154	80 / 176	90 / 198	100 / 220	Days Before Steady State Achieved†
0		62.5‡	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

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

† If no loading dose administered.

‡ 62.5 mcg = 0.0625 mg

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

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

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

Table 6: Daily Maintenance Doses in Children with Normal Renal Function

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

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

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

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

Dosage Adjustment When Changing Preparations: The difference in bioavailability between LANOXIN Injection or LANOXICAPS and LANOXIN Elixir Pediatric or LANOXIN Tablets must be considered when changing patients from one dosage form to another.

Doses of 100 mcg (0.1 mg) and 200 mcg (0.2 mg) of LANOXICAPS are approximately equivalent to 125-mcg (0.125-mg) and 250-mcg (0.25-mg) doses of LANOXIN Tablets and Elixir Pediatric, respectively (see table in CLINICAL PHARMACOLOGY: Pharmacokinetics).

HOW SUPPLIED:

LANOXIN (digoxin) Tablets, Scored 125 mcg (0.125 mg): Bottles of 100 with child-resistant cap (NDC 0173-0242-55) and 1000 (NDC 0173-0242-75); unit dose pack of 100 (NDC 0173-0242-56). Imprinted with LANOXIN and Y3B (yellow).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

LANOXIN (digoxin) Tablets, Scored 250 mcg (0.25 mg): Bottles of 100 with child-resistant cap (NDC 0173-0249-55), 1000 (NDC 0173-0249-75), and 5000 (NDC 0173-0249-80); carton of 12 bottles of 100 (NDC 0173-0249-01); unit dose pack of 100 (NDC 0173-0249-56). Imprinted with LANOXIN and X3A (white).

Store at 15° to 25°C (59° to 77°F) in a dry place.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-282** Date of Submission: **October 21, 1997**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Digoxin Tablets USP, 0.125 mg. 0.25 mg, 0.5 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "℞ only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

   b. We acknowledge your statement that this is a grandfather product and has no existing patent. However, the reference listed drug, Lanoxin® Tablets, (Glaxo Wellcome Inc.), was approved September 30, 1997 and the 1998 Orange Book lists a use exclusivity for congestive heart failure for this drug product which expires September 30, 2000. Please update your patent and exclusivity statements.

   c. Please use the abbreviation "mcg" rather than "µg" throughout your labels and labeling.

   d. We encourage you to use "USP" in association with the established name throughout your labels and labeling.

2. CONTAINER 0.125 mg and 0.25 mg (100s, 1000s, 5000s)
   0.5 mg (100s and 1000s)

   a. See GENERAL COMMENTS (a), (c), and (d) above.

b. Revise your storage temperature recommendation to be the same as the innovator and as seen in your insert labeling:

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

3. INSERT

a. GENERAL COMMENTS

i. See GENERAL COMMENTS (a), (c), and (d) above.

ii. Please note that the insert labeling of the reference listed drug, Lanoxin® Tablets, (Glaxo Wellcome Inc.) has been revised. A copy of this revised insert labeling has been attached for your convenience. Please revise your insert labeling accordingly.

iii. Please improve the quality of print throughout the text of the insert labeling.

iv. Please allow a sufficient left hand margin to facilitate the incorporation of the pages of insert text into the appropriate jacket for the submission (i.e., holes are punched along the left hand margin during the filing process and allowing sufficient left hand margin ensures that no text will be lost).

b. TITLE

You may delete the information immediately below the title. This is found in the HOW SUPPLIED section.

c. DESCRIPTION

i. Revise the molecular weight to be 780.96 as seen in USP 23.

ii. ... and the structural formula shown:

iii. Improve the quality of the structural formula.

iv. Indicate that this drug product contains lactose monohydrate and anhydrous lactose.

v. We note that the Components and Composition statement found on page 1081 states that D&C Yellow #10 Aluminum Lake is present in this drug product while the DESCRIPTION section states "D&C Yellow #10". Please comment and/or revise.

vi. We further note that the DESCRIPTION section and the Components and Composition statement found on page 1081 indicate that the 0.5 mg tablet contains D&C Blue #1 while the "Formulation Comparison For Digoxin Tablets" table on page 1083 indicates that the 0.5 mg tablet contains "Green Lake Blend LB 603". We also note that page 1228 refers to an "FD &C Green Lake Blend LB 603". The Certificate of Analysis for "Lake Blend LB-603" found on page 1231 states that its ingredients are "D&C Yellow #10 Aluminum Lake" and FD&C Blue #1 Aluminum Lake". Please comment and/or revise.

vii. Please list the dyes in the imprinting ink if there are any.

d. INDICATIONS

Revise the section heading to read:

INDICATIONS AND USAGE

e. HOW SUPPLIED

i. Please indicate that the tablets are round and that they are imprinted on the scored side.

ii. Include the dispensing statement as seen on your container labels:

Dispense in a tight, light-resistant container as defined in the USP.

iii. See GENERAL COMMENT (1)(a). Include the symbol "Rx only" or "℞ only".

iv. Include the revision date.

Please revise your container labels and insert labeling, as instructed above, and submit final printed container labels and draft insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of reference listed drug labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-282

CORRESPONDENCE

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

November 24, 1999

NDA ORIG AMENDMENT

N/AF

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA - 40-282 **LABELING AMENDMENT**
Digoxin Tablets

Dear Mr. Sporn:

In reference to the labeling deficiency letter dated November 22, 1999 from Mr. Adolph Vezza, enclosed please find twelve copies of the revised final printed inserts with corrections.

Also, attached are comparisons between the previously submitted and the revised insert with the differences annotated.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax)

Thank you for your attention to this matter.

Sincerely,
Amide Pharmaceutical, Inc.

FOR Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

labeling draft 11/22/99 A. Vezza

November 12, 1999

NDA ORIG AMENDMENT
N/AF

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

LABELING AMENDMENT

RE: ANDA -40-282
Digoxin Tablets

Dear Mr. Sporn:

In reference to the labeling deficiency letter dated November 4, 1999 from Mr. Adolph Vezza, enclosed find twelve copies of revised final printed inserts with corrections.

Also, attached are comparisons between the previously submitted and revised insert with differences annotated.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutical, Inc.

FOR Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

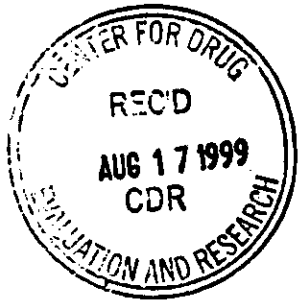
Enc.

NOV 1999

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980



NDA ORIG AMENDMENT

N/A-1

August 11, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

MINOR AMENDMENT

RE: ANDA -40-282
Digoxin Tablets

Dear Mr. Sporn:

In reference to the deficiency letter dated June 18, 1999 and my telephone conversations with Richard Adams, Mark Anderson and Susan Rosencrance, enclosed find our response as follows:

Based on the conference calls between FDA, Amide and Boehringer Ingelheim, the specification for the limit for Methylene Chloride is revised to 2000 ppm. Enclosed in Attachment 1 is a revised copy of the test method and specification for Digoxin raw material.

Deficiencies:

Also, enclosed with this letters are twelve (12) revised copies of final printed insert as recommended in the labeling deficiency dated June 18, 1999 along with the comparative differences annotated from the proposed and revised labeling (Attachment 2).

We would like to thank Mr. Richard Adams, Mr. Mark Anderson and Ms. Susan Rosancrance for their help in coordinating and resolving the issues regarding the specification for Methylene Chloride. Resolving this issue without their help would have been very difficult and we are grateful for their help.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

labeling received
drafted 6/15/99
A. Wejsa

April 12, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/A

MINOR AMENDMENT

RE: ANDA -40-282
Digoxin Tablets

Dear Mr. Sporn:

In reference to the deficiency letter dated March 30, 1999 and my telephone conversation with Mark Anderson and Susan Rosencrance, on April 4, 1999 enclosed find our response as follows:

A. Deficiencies:

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

9/12/99

Also, enclosed with this letters are revised twelve (12) copies of final printed labels and inserts as recommended in the labeling deficiency dated March 30, 1999 along with the comparative differences annotated from the proposed and revised labeling (Attachment 4).

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

FPL

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

ORIG AMENDMENT
N/AC

August 19, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAJOR AMENDMENT

RE: ANDA -40-282
Digoxin Tablets

Dear Mr. Sporn:

In reference to the deficiency letter dated August 7, 1998, enclosed find our response.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
AUG 25 1998
GENERIC DRUGS

001

Page(s) 5

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

8/19/98

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

March 26, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

RE: ANDA - 40-282
DIGOXIN TABLETS

Dear Mr. Sporn:

Per my telephone conversation with Peter Rickman, enclosed find amendment to our pending application for ANDA 40-282, Digoxin Tablets.

Lanoxin Tablets as listed in the Approved Drug Products with Therapeutic Equivalence Evaluation (Orange Book), indicates that Glaxo Wellcome is not currently marketing Lanoxin 0.5 mg Tablets at this time. Therefore, Amide is withdrawing the portion of the ANDA application which relates to Digoxin Tablets 0.5 mg. Our application for Digoxin Tablets 0.125 mg and 0.25 mg are still current.

Please note the change and direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
MAR 27 1998
GENERIC DRUGS

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

January, 28 1998

NEW CORRESP
NC

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NAI
Updated Methods to USP

RE: ANDA - 40-282
DIGOXIN TABLETS

Dear Mr. Sporn:

Per my telephone conversation with Timothy Ames, enclosed find additional information to our pending ANDA 40-282, Digoxin Tablets.

Following changes/additional tests have been made to the pending ANDA since submission :

1. The dissolution method is revised as per the revision in USP

2. Finish product and stability samples are monitored for Degradation products.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
JAN 29 1998
GENERIC DRUGS

ANDA 40-282

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

DEC 11 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated November 18, 1997, and to your correspondence dated November 21, 1997.

NAME OF DRUG: Digoxin Tablets USP, 0.125 mg, 0.25 mg and 0.5 mg

DATE OF APPLICATION: October 21, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 21, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Timothy Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (201) 890-1440
Fax (201) 890-7980

October 21, 1997

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA - ORIGINAL APPLICATION
DIGOXIN TABLETS 0.125 mg, 0.25 mg and 0.5 mg

Dear Dr. Williams:

Enclosed please find Amide Pharmaceutical's original Drug Application for Digoxin Tablets and a transmittal letter (and one copy) describing same.

Kindly, have the copy of the transmittal letter stamped "filed" and return it to our courier who has been instructed to wait.

Thank you for your attention to this matter.

Very truly yours,

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (201) 890-1440
Fax (201) 890-7980

October 21, 1997

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA - ORIGINAL APPLICATION
DIGOXIN TABLETS USP

Dear Mr. Sporn:

Pursuant to section 505 (b) of the Food, Drug and Cosmetic Act and amendments thereto and in conformance with 21 CFR section 310.500 (a) et seq., we are submitting herewith, in duplicate, and Original Abbreviated New Drug Application for the drug, Digoxin Tablets USP.

The ANDA complies with and provides the CDER all of the documents and information required under Section 310.500. In addition, please be advised that currently Amide markets Digoxin Tablets in all of the above referenced strengths, it has received batch certification from the FDA and has currently exempted Amide from further batch certification. Further, Amide's facility, production and testing controls for these products have all been inspected by the FDA.

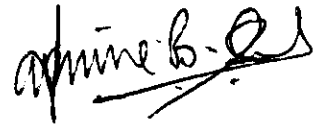
Included in the file are:

1. All information required by Form 356-H including:
   a) Form 356-H
   b) Archival Copy (blue folder) - 6 Volumes
   c) Review Copy - CMC (red folder) - 2 Volume (Volumes 1 and 2)
   d) Review Copy - Bioeqivalence (orange folder) - 4 Volumes (Volumes 3 to 6)
   e) Three copies of Analytical Method and Validation Report
   f) Twelve copies of final printed labeling for all three strengths.
   g) Diskette containing the concentration and parameters data for the bioequivalency study. The file name is called FDA.1

2. A copy of CMC Section of the ANDA; the third copy is being sent to the FDA's Newark District Office, Attn: Regina Brown as required under FDA guidelines.

If you or your staff have any question, please feel free to contact us. Your review of this Abbreviated New Drug Application would be greatly appreciated.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.



Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

cc: Regina Brown
FDA,/Newark District Office (w/CMC section of ANDA only)