

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-648

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW
(505(b)(2) NDA)

NDA number: 21-648
Date of submission: Apr 14, 2003
Sponsor : Roxane Laboratories, Inc.
1809 Wilson Road, Columbus Ohio 43228

Manufacturer for drug substance :

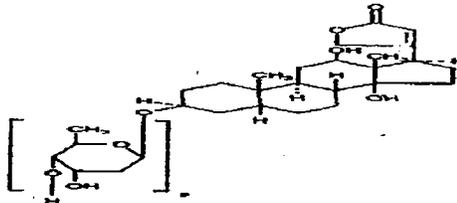
Reviewer : Belay Tesfamariam, PhD
Division : Cardio-Renal Drug Products, HFD-110
Review completion date: 11/27/03

Drug:
Trade name: Digoxin Elixir USP
Generic name: Cordioxil, davoxin, Digacin, Dilanacin, Dixina, Dokim, Dynamox, Eudigox, Lanacordin, Lanicor, Lanoxin, Lenoxcaps, Longdigox, Neo-Dioxanin, Rougoxin, Stillacor, Vanoxin
Chemical name: 3 β -{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 β , 14-dihydroxy-5 β -card-20(22)-enolide

Molecular formula: C₄₁H₆₄O₁₄

Molecular weight: 780.95

Structure:



Relevant INDs/NDAs/DMFs: NDA 20-405 (approved 9/30/97) Lanoxin® 0.25 mg tablets,
Lanoxin® Elixir pediatric 0.05 mg/ml (GlaxoSmithKline)

Drug class: Cardiac glycoside (digitalis)

Indication: Treatment of heart failure and control of ventricular response rate in patients with chronic atrial fibrillation

Clinical formulation: Digoxin 0.05 mg/ml (50 μ g),
(inactive ingredients: alcohol 10%, methylparaben 0.15%, propylparaben 0.02%)

Route of administration: Oral

Proposed use: Formulated for oral use in infants and children

Summary

I. Background :

The objective of this NDA is to seek approval for the pediatric use of Digoxin Elixir 0.05 mg/ml for the treatment of mild to moderate heart failure and atrial fibrillation. Roxane Laboratories, Inc. has marketed this formulation since 1988 under the brand name Digoxin Elixir USP, 0.05 mg/ml.

In the November 24, 2000 Federal Register, the FDA notified drug companies that it required submission of drug applications and bioavailability tests for all oral digoxin products. Roxane submitted a response on February 16, 2001, stating that the product was medically necessary and should remain on the market until such time that an NDA could be submitted to the FDA. In a meeting held on March 27, 2002 to discuss the submission of a 505(b)(2), the Division of Cardio-Renal Drug Products agreed to defer regulatory action because an NDA was being actively pursued, and the product is of a medically necessary nature.

This submission references data in the approved NDA 20-405 for use of Lanoxin tablets for treatment of heart failure. Preclinical and clinical information are extensively cross-referenced. There are no new preclinical tests submitted as part of this NDA

II. Recommendations

A. Recommendation on Approvability: Approvable

B. Recommendation for Nonclinical Studies: None

C. Recommendations on Labeling: Update based on recent review of the literature.

Digoxin Elixir is expected to have a safety and efficacy profile similar to that of currently marketed formulations, and the labeling for the elixir closely resembles the labeling in NDA 20-405.

- Digoxin is a substrate of the multidrug transporter P-glycoprotein (Pgp), and therefore absorption and the subsequent elimination into the bile and small intestine may be influenced by drugs that affect these proteins.
- 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.
- Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

III. Summary of Nonclinical Findings:

A. Brief Overview of Pharmacology:

The active ingredient, digoxin, inhibits Na-K ATPase leading to an increase in the intracellular concentration of Na followed by stimulation of Na-Ca exchange resulting in an increase in the intracellular Ca concentration. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by the autonomic nervous system. The autonomic effects include: (i) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (ii) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system.

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 activation of the sympathetic nervous system and renin-angiotensin system; (3) decreased conduction velocity through the AV node (vagomimetic effect); and (4) reduces catecholamine uptake, rendering more exposure of blood vessels to catecholamines. 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 arrhythmia are related to its vagomimetic actions.

In comparison with ouabain, another cardiac glycoside, which can increase blood pressure, digoxin exhibits antihypertensive effects suggesting that N-K pump inhibition is not the exclusive mediator of the hemodynamic effects of these cardiac glycosides.

B. Pharmacokinetics:

Absorption of digoxin from Elixir pediatric formulation is estimated to be 70% - 85% compared to an identical intravenous dose of digoxin, i.e., 62.5 µg Lanoxin Elixir pediatric equivalent and 62.5 µg Lanoxin tablets are equivalent to 50 µg Lanoxin injection/IV. Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. Approximately 25% of digoxin in the plasma is bound to protein. Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3β-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. In rats, oral administration of ketoconazole (inhibitor of CYP3A and P-glycoprotein) increased digoxin (iv) plasma concentrations, rate of absorption and bioavailability. Although the effects of ketoconazole on AUC could be explained by inhibition of both CYP3A and Pgp, the decreased mean absorption time can only be explained by inhibition of P-glycoprotein in the intestine (Pharmacol 56:308, 1998). In human studies, intestinal p-glycoprotein mediates drug elimination after IV administration from systemic circulation into the gut (Clin Pharmacol Ther 73:223, 2003). 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.

Digoxin is excreted mainly in urine, principally as unchanged drug, by glomerular filtration and active tubular secretion (elimination $t_{1/2}$ ~ 2 days). Digoxin is not effectively removed from the

body because most of the drug is bound to tissue and does not circulate in the blood. Children require higher doses of digoxin on a per kilogram basis than adults, because of their efficient renal function.

The amount of digoxin eliminated daily is a function of the amount of drug in the body, i.e., the quantity of digoxin eliminated is proportional to the total body content (1st-order kinetics). Therapeutic plasma concentrations of digoxin in adults are generally 0.5 - 2 ng/ml.

C. Brief Overview of General Toxicology:

Roxane Laboratories refers to the approved digoxin tablets, NDA 20-405 (approved 9/30/97) for safety concerning non-clinical pharmacology and toxicology. A literature search since 1997 on publications on digoxin is reviewed. The studies covered a wide range of the pharmacologic effects of digoxin, although none appeared to be of value in assessing potential human risk of the elixir.

In high doses, digoxin increases sympathetic outflow from the CNS. This increase in sympathetic activity may be an important factor in digitalis toxicity as manifested by cardiac disturbances (arrhythmia, heart block, asystole, atrial tachycardia), CNS manifestations (apathy, confusion), and gastrointestinal disturbances (vomiting, diarrhea, intestinal hemorrhage).

Genetic Toxicology, Carcinogenicity, Reproductive Toxicology:

No articles reported on carcinogenicity, mutagenicity, genotoxicity, or reproductive toxicity.

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.

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

D. Nonclinical Safety Issues Relevant to Clinical Use:

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect.

Cardiac arrhythmias, including sinus bradycardia and atrial tachycardia should be closely monitored in infants and children. Serum digoxin levels should not be acquired during digitalization because they are high (prior to tissue distribution) and misleading.

Digoxin is a P-glycoprotein substrate, and therefore absorption and the subsequent elimination into the bile and small intestine may be influenced by drugs that affect the P-glycoprotein.

NDA21-648

Reviewer: _____

Supervisor: Concurrence - _____

Non-concurrence -
(see memo attached) _____

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/s/

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PHARMACOLOGIST