



Jeff Sampere
Vice President, Marketing
Covis Pharmaceuticals
1513 Walnut Street, Suite 270
Cary, NC 27511

RE: NDA #020405
LANOXIN[®] (digoxin) Tablets, for oral use
MA #34

Dear Mr. Sampere:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a physician letter (LANO0050) (letter) for LANOXIN[®] (digoxin) tablets, for oral use (Lanoxin) submitted by Covis Pharmaceuticals (Covis) under cover of Form FDA 2253. The letter is false or misleading because it omits and minimizes important risk information associated with the drug, makes misleading superiority claims, and suggests that the drug is useful in a broader range of patients or conditions than has been substantiated for Lanoxin. Thus, the letter misbrands Lanoxin within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative of the FD&C Act. 21 U.S.C. 352(a); 321(n); 331(a), and implementing regulation 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i); (e)(7)(viii). The letter also provides evidence that Lanoxin is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Lanoxin misbranded or otherwise makes its distribution violative. See 21 U.S.C 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115. In addition, Covis did not comply with 21 CFR 201.100(d).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Lanoxin.¹ According to the FDA-approved product labeling (PI)², Lanoxin is indicated for (emphasis in original):

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

² The PI submitted with the letter on Form FDA 2253 was dated November 2011. However, the letter was submitted on March 9, 2013, with a listed dissemination date of March 1, 2013; the most current version of the FDA-approved PI as of those dates is the August 2012 version, and that is the version referred to in this letter.

Heart Failure in Adults

LANOXIN is indicated for the treatment of mild to moderate heart failure in adults. LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by improved exercise capacity and decreased heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, LANOXIN should be used in combination with a diuretic and an angiotensin-converting enzyme (ACE) inhibitor.

Heart Failure in Pediatric Patients

LANOXIN increases myocardial contractility in pediatric patients with heart failure.

Atrial Fibrillation in Adults

LANOXIN is indicated for the control of ventricular response rate in adult patients with chronic atrial fibrillation.

Lanoxin is associated with serious risks. According to the PI, Lanoxin is contraindicated in patients with ventricular fibrillation and a known hypersensitivity reaction to digitalis. In addition, the PI contains Warnings and Precautions regarding ventricular fibrillation in patients with accessory AV pathway (Wolff-Parkinson-White Syndrome), sinus bradycardia and sino-atrial block, digoxin toxicity, decreased cardiac output in patients with preserved left ventricular systolic function, reduced efficacy in patients with hypocalcemia, risk of ventricular arrhythmias during electrical cardioversion, altered response in thyroid disorders and hypermetabolic states, risk of ischemia in patients with acute myocardial infarction, and vasoconstriction in patients with myocarditis. The most common adverse reactions associated with Lanoxin were cardiac toxicity, gastrointestinal disturbances, and CNS and other toxicity.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The letter is misleading because it includes numerous efficacy claims for Lanoxin but fails to include important risk information associated with the drug. Specifically, the letter completely omits all information from the CONTRAINDICATIONS section of the PI, as well as the risks of ventricular fibrillation in patients with accessory AV pathway (Wolff-Parkinson-White Syndrome), sinus bradycardia and sino-atrial block, decreased cardiac output in patients with preserved left ventricular systolic function, reduced efficacy in patients with hypocalcemia, risk of ventricular arrhythmias during electrical cardioversion, altered response in thyroid disorders and hypermetabolic states, risk of ischemia in patients with acute myocardial infarction, and vasoconstriction in patients with myocarditis, as described in the WARNINGS AND PRECAUTIONS section of the PI.

Additionally, while the letter presents some information regarding digoxin toxicity associated with Lanoxin, it omits material information from the WARNINGS AND PRECAUTIONS section of the PI regarding this risk. For example, the letter fails to disclose that signs and symptoms of digoxin toxicity include visual changes and that advanced age, low body weight,

impaired renal function, and electrolyte abnormalities may predispose patients to digoxin toxicity.

Furthermore, the letter is misleading because it presents some of the most common adverse events of Lanoxin, such as “gastrointestinal and cardiac disturbances,” but completely omits other significant common adverse reactions associated with the drug. According to the ADVERSE REACTIONS section of the PI, “[t]he overall incidence of adverse reactions with digoxin has been reported as 5 to 20%, with 15 to 20% of adverse events considered serious. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse events.”

We acknowledge that the letter includes the statement, “Please see full prescribing information including contraindications, warnings, and precautions at covispharma.com under products and then Lanoxin Tablets.” However, this does not mitigate the misleading omission of important risk information from the letter.

Moreover, promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. The letter prominently presents efficacy claims in the body of the letter with selected terms bolded. In contrast, the limited risk information that is included is presented on the back side of the letter after the signature block, in significantly smaller type print, and with a reference to actively search out a separate source for the complete risk information. As such, the letter fails to present the risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug.

By omitting and minimizing important risk information, the letter misleadingly suggests that Lanoxin is safer than has been demonstrated.

Misleading Superiority Claims

The letter includes the following claims (emphasis in original):

- “Physicians, like yourself, have many options when choosing a medication to treat their patients, including prescribing a brand or a generic. With some medications the difference may have no impact. But with others, such as narrow therapeutic index products, you may want to consider all your options.”
- “Narrow therapeutic index (NTI) drugs are agents for which small changes in systemic concentration can lead to significant changes in pharmacodynamics response. This may result in potentially sub-therapeutic or toxic effects, particularly in patients with advanced age, co-morbid illness, or those receiving multiple medications.”^[3]
- “Branded **Lanoxin**[®] has been manufactured by the same organization for over 78 years, and has been made at the same plant for over 30 years with no disruption to supply due to any manufacturing concerns. It is critical to insure that Lanoxin/digoxin

^[3] Burns M. Management of narrow therapeutic index drugs. *J Thromb Thrombolysis*. 1999 Apr;7(2):137-43

tablets are manufactured to specific tolerances so that the patient does not receive either too much or too little of the drug. In fact, in the past 5 years there have been two manufacturers that have left the digoxin market because of manufacturing issues^[4,5] and one company has suspended manufacturing.”^[6]

- “It is important to consider all the options when prescribing a narrow therapeutic index product. A small change in the dosage can have an impact on safety and efficacy. **Lanoxin**[®] is manufactured under strict standards to provide clinical benefits within a narrow therapeutic index.”^[7,8]

The totality of this presentation misleadingly suggests that Lanoxin is superior in safety and efficacy to generic formulations of digoxin, thereby suggesting they are not therapeutically equivalent to Lanoxin. FDA has reviewed and approved a number of therapeutically equivalent formulations of digoxin tablets and digoxin injections and granted an “AB” or “AP” rating, respectively.⁹ These ratings mean that the Agency considers the products therapeutically equivalent; one can be substituted for the other with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Unless and until the Agency’s determination is changed or reversed, any promotion suggesting a lack of equivalence between Lanoxin and products deemed to be therapeutically equivalent are considered false or misleading.

Broadening of Patient Population or Condition

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The letter contains the following claims (emphasis in original):

- “**Lanoxin**[®] is indicated. . . for the control of ventricular response rate in patients with chronic atrial fibrillation.”
- “LANOXIN is also indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.”

^[4] FDA - Actavis Totowa (formerly known as Amide Pharmaceutical, Inc.) recalls all lots of Bertek and UDL Laboratories Digitek® (digoxin tablets, USP) as precaution, Recall – Firm Press Release, April 25, 2008 (<http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2008/ucm112435.htm>)

^[5] FDA - Caraco Pharmaceutical Laboratories, Ltd. Announces a Nationwide Voluntary Recall of All Lots of Digoxin Tablets Due to Size Variability, Recall – Firm Press Release, March 31, 2009 (<http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2009/ucm128443.htm>)

^[6] FDA – Department of Health and Human Service, Inspections, Compliance, Enforcement, and Criminal Investigations, West-Ward Pharmaceuticals Corporation Warning Letter, February 3, 2012 (<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm291643.htm>)

^[7] Packer M, Gheorghiadu M, Young JB, et al; for the RADIANCE study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *N Engl J Med.* 1993;329:1-7.

^[8] Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK; on behalf of the PROVED Investigative Group. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. *J Am Coll Cardiol.* 1993;22:955-962.

⁹ Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through March 2013. Available at <http://www.fda.gov/cder/ob/default.htm> (last accessed May 8, 2013).

These claims misleadingly suggest that Lanoxin is useful in treating all patients with chronic atrial fibrillation, when this has not been demonstrated by substantial evidence or substantial clinical experience. As described above, Lanoxin's approved indication for the control of ventricular response rate in patients with chronic atrial fibrillation is limited to **adult** patients. Moreover, the USE IN SPECIFIC POPULATIONS section of the PI states, "The safety and effectiveness of LANOXIN in the control of ventricular rate in children with atrial fibrillation . . . have not been established." Information sufficient to support use in the broader patient population or condition suggested in this letter has not been submitted to FDA in an application, nor are we otherwise aware of substantial evidence or substantial clinical experience that would support it. These claims in the letter also provide evidence that Lanoxin is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use.

Use of Outdated Product Labeling

It appears the letter was disseminated with an outdated version of the PI, in violation of 21 CFR 201.100(d). The PI submitted with the promotional piece on Form FDA 2253 was dated November 2011. However, the listed dissemination date of the letter was March 1, 2013; the most current version of the FDA-approved PI as of March 1, 2013 was the August 2012 version, not the November 2011 version.

Conclusion and Requested Action

For the reasons discussed above, the letter misbrands Lanoxin within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a), and implementing regulation 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i); (e)(7)(viii). The letter also provides evidence that Lanoxin is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Lanoxin misbranded or otherwise makes its distribution violative. See 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5, 201.100; 201.115. Furthermore, Covis did not comply with 21 CFR 201.100(d).

OPDP requests that Covis immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before December 23, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Lanoxin that contain statements such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Amundson Avenue, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #34 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Lanoxin complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Emily Baker, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Amy Toscano, PharmD, RAC, CPA
Team Leader
Office of Prescription Drug Promotion

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/s/

EMILY K BAKER
12/09/2013

AMY TOSCANO
12/09/2013