DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 009330/S-030 **SUPPLEMENT APPROVAL**

Covis Injectables S.a.r.l.
c/o Cardinal Health Regulatory Sciences
Attention: Todd Phillips, Pharm.D., RAC
Director, Executive Consultant, US Agent
7400 W. 110th Street, Suite 300
Overland Park, KS 66210

Dear Dr. Phillips:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 3, 2015, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lanoxin (digoxin) Injection and Lanoxin (digoxin) Injection Pediatric, 0.1 mg/mL and 0.25 mg/mL

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was deleted from the second bullet:

   - ~~Many drug interactions.~~ The potential for drug-drug interactions must be considered prior to and during drug therapy. See full prescribing information. (7.2, 7.3, 12.3)

2. Under **DRUG INTERACTIONS**, the following text was added/deleted:

   7.1 P-Glycoprotein (PGP) Inducers/Inhibitors

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

3. Under **DRUG INTERACTIONS**, the following text was deleted from the table:

Digoxin concentrations increased greater than 50%			
	Digoxin Serum Concentration Increase	**Digoxin AUC Increase**	**Recommendations**
Quinidine	NA	54-83%	Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30-50% or by modifying the dosing frequency and continue monitoring.
Ritonavir	NA	86%	
Digoxin concentrations increased less than 50%			
Amiodarone	17%	40%	Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing the dose by approximately 15-30% or by modifying the dosing frequency and continue monitoring.
Propafenone	28%	29%	
Quinine	NA	34-38%	
Spironolactone	NA	44%	
Verapamil	NA	24%	
~~**No significant Digoxin exposure changes**~~			
~~Please refer to section 12 for a complete list of drugs that were studied but reported no significant changes on digoxin exposure.~~			~~No additional actions are required.~~

4. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was deleted:

~~*Drug-drug Interactions*~~

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

~~clarithromycin, carvedilol, isradipine, losartan and rifampin~~

5. Under **PATIENT COUNSELING INFORMATION**, the following text was deleted from the 1st, 2nd, and 7th bullets:

- Advise patients that digoxin is ~~a cardiac glycoside~~ used to treat heart failure and heart arrhythmias.
- Instruct patients to take this medication as directed ~~by their physician~~.
- ~~Suggest to~~ Instruct the patient to monitor and record their heart rate and blood pressure daily.

6. The revision date was updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

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

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

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

PROMOTIONAL MATERIALS

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

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

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

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

REPORTING REQUIREMENTS

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

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
07/28/2015