DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020405/S-013

SUPPLEMENT APPROVAL

Concordia Pharmaceuticals Inc.
c/o Mapi USA, Inc.
Attention: Mandy Dorsey
Associate Director, US Regulatory
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Ms. Dorsey:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 12, 2016 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lanoxin (digoxin) 0.0625 mg, 0.125 mg, 0.1875mg, and 0.25mg Tablets.

We also refer to our December 1, 2016 Approval letter for Supplement 13 (S-013). The December 1st Approval letter and appended labeling contained a formatting error in Table 7.2 making some of the text unreadable. This letter corrects the error and supersedes the December 1, 2016 Approval letter. The date of the action remains December 1, 2016.

This supplemental new drug application provides for revisions to the approved label as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. Under **DRUG INTERACTIONS,** the following text was deleted from the table in section 7.2:

Digoxin concentrations increased greater than 50%			
	Digoxin Serum Concentration	**Digoxin AUC Increase**	**Recommendations**
Amiodarone	70%	NA	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.
Captopril	58%	39%	
Clarithromycin	NA	70%	
Dronedarone	NA	150%	
Gentamicin	129-212%	NA	
Erythromycin	100%	NA	
Itraconazole	80%	NA	
Lapatinib	NA	180%	
~~Nitrendipine~~	~~57%~~	~~15%~~	
Propafenone	NA	60-270%	
Quinidine	100%	NA	

Ranolazine	50%	NA	
Ritonavir	NA	86%	
Telaprevir	50%	85%	
Tetracycline	100%	NA	
Verapamil	50-75%	NA	
Digoxin concentrations increased less than 50%			
Atorvastatin	22%	15%	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.
Carvedilol	16%	14%	
Conivaptan	33%	43%	
Diltiazem	20%	NA	
Telmisartan	20-49%	NA	
Ticagrelor	31%	28%	
Tolvaptan	30%	20%	
Trimethoprim	22-28%	NA	
Digoxin concentrations increased, but magnitude is unclear			
Alprazolam, azithromycin, cyclosporine, diclofenac, diphenoxylate, epoprostenol, esomeprazole, ibuprofen, ketoconazole, lansoprazole, metformin, omeprazole			Measure serum digoxin concentrations before initiating concomitant drugs. Continue monitoring and reduce digoxin dose as necessary.

1. Under **DRUG INTERACTIONS,** the following text was added to the table in section 7.3:

Drugs that Affect Renal Function	A decline in GFR or tubular secretion, as from ACE inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs [NSAIDs], COX-2 inhibitors may impair the excretion of digoxin.	
Antiarrthymics	Dofetilide	Concomitant administration with digoxin was associated with a higher rate of torsades de pointes.
	Sotalol	Proarrhythmic events were more common in patients receiving sotalol and digoxin than on either alone; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digoxin.
	Dronedarone	Sudden death was more common in patients receiving digoxin with dronedarone than on either alone; it is not clear whether this represents an interaction or is related to the presence of advanced heart disease, a known risk factor for sudden death in patients receiving digoxin.
Parathyroid Hormone Analog	Teriparatide	Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Teriparatide transiently increases serum calcium.
Thyroid supplement	Thyroid	Treatment of hypothyroidism in patients taking digoxin may increase the dose requirements of digoxin.
Sympathomimetics	Epinephrine Norepinephrine Dopamine	Can increase the risk of cardiac arrhythmias.
Neuromuscular Blocking Agents	Succinylcholine	May cause sudden extrusion of potassium from muscle cells, causing arrhythmias in patients taking digoxin.
Supplements	Calcium	If administered rapidly by intravenous route, can produce serious arrhythmias in digitalized patients.
Beta-adrenergic blockers and calcium channel blockers		Additive effects on AV node conduction can result in bradycardia and advanced or complete heart block.
Hyperpolarization-activated cyclic nucleotide-gated channel blocker	ivabradine	Can increase the risk of bradycardia

2. The revision date was updated.

3. The manufacturer information was updated to reflect transfer of ownership to Concordia.

There are no other changes from the last approved package insert

APPROVAL & LABELING

We have completed our review of this supplemental application 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, text for the patient package insert, Medication Guide),

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 that include labeling changes 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).

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, RAC
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 I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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
12/01/2016