DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-361/S-009

SUPPLEMENT APPROVAL

Salix Pharmaceuticals, Inc
Attention: Gail Glifort
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your supplemental new drug application dated February 6, 2009, received February 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xifaxan (rifaximin) Tablets, 220 mg.

Your submissions dated June 3 and June 9, 2010, constitute a complete response to our August 7, 2009 complete response letter.

We also acknowledge your submission dated October 27, 2010.

This supplemental new drug application provides for the following revisions to the labeling for Xifaxan (additions are noted with underline and deletions are noted with ~~strikethrough~~):

Section **8 USE IN SPECIFIC POPULATIONS/8.1 Pregnancy** is revised as follows:

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Rifaximin has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity. XIFAXAN tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

~~XIFAXAN should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose for travelers' diarrhea [600 mg/day], and approximately 1.3 to 2.6 times the clinical dose for hepatic encephalopathy [1100 mg/day], adjusted for body surface area). Rifaximin was teratogenic in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the clinical dose for travelers' diarrhea [600 mg/day], and approximately 1.1 to 18 times the clinical dose for hepatic encephalopathy [1100 mg/day], adjusted for body surface area). These effects~~

~~include cleft palate, agnatha, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae.~~

Administration of rifaximin to pregnant rats and rabbits at dose levels that caused reduced body weight gain resulted in eye malformations in both rat and rabbit fetuses. Additional malformations were observed in fetal rabbits that included cleft palate, lumbar scoliosis, brachygnathia, interventricular septal defect, and large atrium.

The fetal rat malformations were observed in a study of pregnant rats administered a high dose that resulted in 16 times the therapeutic dose to diarrheic patients or 1 times the therapeutic dose to patients with hepatic encephalopathy (based upon plasma AUC comparisons). Fetal rabbit malformations were observed from pregnant rabbits administered mid and high doses that resulted in 1 or 2 times the therapeutic dose to diarrheic patients or less than 0.1 times the dose in patients with hepatic encephalopathy, based upon plasma AUC comparisons.

Post-natal developmental effects were not observed in rat pups from pregnant/lactating female rats dosed during the period from gestation to Day 20 post-partum at the highest dose which resulted in approximately 16 times the human therapeutic dose for travelers' diarrhea (based upon AUCs) or approximately 1 times the AUCs derived from therapeutic doses to patients with hepatic encephalopathy.

We have completed our review of this supplemental application, as amended. This supplement is approved, effective on the date of this letter, for use as recommended in the package insert attached to this letter, which is identical to the package insert submitted on October 27, 2010.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 pending "Changes Being Effected" (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.

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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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, call Ms. June Germain, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package insert

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

/s/

RENATA ALBRECHT
11/15/2010