DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021361/S-012

SUPPLEMENT APPROVAL

Salix Pharmaceutical, Inc.
Attention: Gail Glifort
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh NC, 27615

Dear Ms. Glifort:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xifaxan (rifaximin) tablets, 550 mg.

We acknowledge receipt of your amendments dated June 8, 2010, June 16, 2010, June 18, 2010, August 18, 2010, September 7, 2010, September 15, 2010, October 08, 2010, October 15, 2010, October 21, 2010, October 25, 2010, November 17, 2010, December 22, 2010, January 5, 2011, January 6, 2011, February 22, 2011, March 4, 2011, April 12, 2011, October 13, 2011, August 29, 2014, September 17, 2014, September 27, 2014, October 17, 2014, October 30, 2014, November 3, 2014, November 7, 2014, November 17, 2014, November 21, 2014, December 1, 2014, December 5, 2014, December 19, 2014, December 23, 2014, January 6, 2015, January 16, 2015, January 23, 2015, February 6, 2015, March 6, 2015, March 12, 2015, March 13, 2015, March 23, 2015, March 31, 2015, April 7, 2015, May 1, 2015, May 15, 2015, and May 26, 2015.

The August 29, 2014, submission constituted a complete response to our March 7, 2011, action letter.

This "Prior Approval" supplemental new drug application proposes an indication for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

APPROVAL & LABELING

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

WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and

Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015.

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 that includes 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on May 1, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021361/S-012**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 months to less than 6 years because necessary studies are impossible or highly impracticable. This is because irritable bowel syndrome (IBS) is uncommon in this age group, and it may be difficult to diagnose younger children as they may not be able to report IBS-related symptoms accurately and consistently.

We are deferring submission of your pediatric studies for ages 6 to less than 17 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

PMR 2900-1: Conduct a pharmacokinetic, pharmacodynamics, tolerability and dose ranging study in subjects 6 years through 17 years, to assess safety and to determine the doses to be used in the efficacy study. Age-specific endpoints, i.e. a clinical outcome assessment utilizing Patient Reported Outcomes (PROs) or a PRO instrument to evaluate efficacy of rifaximin for the treatment of irritable bowel disease (IBS) in children, should be developed.

Final Protocol Submission:	11/30/2016
Study Completion:	09/30/2018
Final Report Submission:	03/31/2019

PMR 2900-2: Conduct a randomized, controlled, double-blind study to determine the safety and efficacy of rifaximin in pediatric patients 6 years through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D).

Final Protocol Submission:	12/31/2018
Study Completion:	12/31/2022
Final Report Submission:	12/31/2023

Submit the protocol(s) to your IND 059133, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When

submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

> **PMC 2900-3**: Conduct in vitro studies to properly determine the IC_{50} values for the inhibition of OATP1B1, OATP1B3, and OATP1A2 by rifaximin. The in vitro study results will determine the need for subsequent clinical assessments of drug interactions by rifaximin.

The timetable you submitted via email on April 28, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/31/2015
Study Completion:	04/30/2016
Final Report Submission:	06/30/2016

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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
> Office of Prescription Drug Promotion (OPDP)
> 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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

ANDREW E MULBERG
05/27/2015