



NDA 022554

**NDA APPROVAL**

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

Dear Ms. Glifort:

Please refer to your new drug application (NDA) dated and received on June 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xifaxan® (rifaximin) 550mg Tablets for oral use.

We acknowledge receipt of your submissions dated June 24, August 4, August 7, August 11, September 17, October 12, November 27, December 21, and December 23, 2009; and January 5, January 25, January 26, February 3, February 5, February 8, March 11, March 23 and March 24, 2010.

This new drug application provides for the use of Xifaxan (rifaximin) 550mg Tablets for reduction in the risk of overt hepatic encephalopathy (HE) recurrence in patients  $\geq$  18 years of age.

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

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit 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). These revisions are terms of the NDA approval. For administrative purposes, please designate this submission "**SPL for approved NDA 022554.**"

### **CARTON AND IMMEDIATE CONTAINER LABELS**

We acknowledge your March 23, 2010 (received on March 24, 2010), submission containing final printed carton and container labels.

## **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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since Xifaxan (rifaximin) was approved on October 25, 2002, and as a result of the review of this new drug application for a new indication for Xifaxan (rifaximin), we have become aware of the potential safety signals of hepatotoxicity and change in gastrointestinal flora with resulting antibiotic resistance in patients treated with Xifaxan (rifaximin). Therefore, we consider this information to be “new safety information” as defined in FDAAA.

Xifaxan is a member of the rifamycin class of antibiotics, which are known to cause liver dysfunction. Xifaxan (rifaximin) exposure is increased in patients with severe hepatic impairment, especially those that are exposed to chronic treatment. Animal toxicity studies have not been conducted to show the effects of systemic exposures that may be seen in patients with severe hepatic impairment. The clinical trials submitted as part of this application did not include patients with the most severe hepatic impairment (Model for End-Stage Liver Disease [MELD] scores >25). Therefore, there is a potential for worsening hepatic function in patients with severe hepatic impairment.

In addition, with this expanded indication for the long term use of Xifaxan (rifaximin), there is also the potential for changes in gastrointestinal flora and the development of antibiotic resistance. The clinical trial submitted as part of this application demonstrated an increased risk of *C. difficile* infections in the Xifaxan (rifaximin) treatment group, and no data on potential antibiotic resistance was collected.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks described in detail above.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

**1615-1** A chronic oral nonclinical toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

The timetable you submitted on March 24, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date: 12/31/2010  
Study Completion Date: 12/31/2012  
Final Report Submission Date: 06/30/2013

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of worsening hepatic function in patients with severe hepatic impairment who are exposed to chronic Xifaxan (rifaximin) treatment and the potential for change in gastrointestinal flora and development of antibiotic resistant organisms with chronic use of rifaximin.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

**1615-2** A randomized, controlled clinical trial to evaluate the safety of rifaximin in patients with hepatic encephalopathy classified as Child-Pugh C, MELD > 19, and MELD  $\geq$  25 hepatic impairment.

The timetable you submitted on March 24, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: 04/30/2011  
Trial Completion Date: 06/30/2014  
Final Report Submission Date: 12/31/2014

**1615-3** A pharmacokinetic trial in patients with severe hepatic impairment (MELD 19 - 25 and MELD > 25). This may be performed as a sub study in the ongoing Phase 3 trial (RFHE3002, A multicenter, open label trial to evaluate the long term safety and tolerability of rifaximin 550 mg BID in subjects with a history of hepatic encephalopathy), or as part of the required clinical trial described under PMR 1615-2.

The timetable you submitted on March 24, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date: 04/30/2011  
Trial Completion Date: 06/30/2014  
Final Report Submission Date: 12/31/2014

**1615-4** A pharmacokinetic trial in patients with concurrent renal insufficiency and liver impairment to determine the extent of elevation of systemic exposure of rifaximin which may lead to worsening of hepatic function. The PK data should be collected and analyzed by the degree of renal insufficiency (e.g. creatinine clearance) within a Child-Pugh class/and by MELD score. A population PK approach will be acceptable.

The timetable you submitted on March 24, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date: 04/30/2011  
Trial Completion Date: 06/30/2014  
Final Report Submission Date: 12/31/2014

**1615-5** A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora. In vitro susceptibility testing to rifaximin and other antimicrobial drugs must be included.

The timetable you submitted on March 24, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: 04/30/2011  
Trial Completion Date: 06/30/2014  
Final Report Submission Date: 12/31/2014

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and insert 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any

study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS  
UNDER SECTION 506B**

We remind you of your postmarketing commitments included in your submission dated March 24, 2010. These commitments are listed below.

- 1615-6** A randomized, controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt hepatic encephalopathy.

The timetable you submitted on March 24, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: 12/31/2010  
Trial Completion Date: 12/31/2013  
Final Report Submission Date: 06/30/2014

- 1615-7** An in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) of rifaximin pharmacokinetics in healthy subjects.

The timetable you submitted on March 24, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date: 12/31/2010  
Study Completion Date: 10/31/2011  
Final Report Submission Date: 04/30/2012

- 1615-8** An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.

The timetable you submitted on March 24, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date: Report in draft  
Study Completion Date: Completed  
Final Report Submission Date: 06/30/2010

Submit clinical protocols to your IND 059133 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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>.

Please submit one market package of the drug product when it is available.

### **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 NDA 021361 and to [CDERMedWatchSafetyAlerts@fda.hhs.gov](mailto:CDERMedWatchSafetyAlerts@fda.hhs.gov), and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B-05  
5600 Fishers Lane  
Rockville, MD 20857

### **REPORTING REQUIREMENTS**

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

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 021361 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796-4147.

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, MD, MPH  
Deputy Director, Safety  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:

Contents of Package Insert  
Contents of Carton and Container Labeling

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22554

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ORIG-1

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SALIX  
PHARMACEUTICA  
LS INC

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XIFAXAN

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOYCE A KORVICK

03/24/2010