NDA 21361/S-031

SUPPLEMENT APPROVAL AND FULFILLMENT OF POSTMARKETING COMMITMENT

Salix Pharmaceuticals Inc.
Attention: Sean Humphrey
Director, Global Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Mr. Sean Humphrey,

Please refer to your supplemental new drug application (sNDA) dated and received on September 22, 2023, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xifaxan (rifaximin) tablet.

We also refer to our Safety Labeling Change Notification letter dated July 18, 2023, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for Xifaxan. This information pertains to the risk of recurrence of overt hepatic encephalopathy (HE).

This supplemental new drug application provides for revisions to the labeling for Xifaxan. The attached agreed-upon labeling includes the following changes:

- Reversion to the original labeling language in subsection **1.2 Indications and Usage/Hepatic Encephalopathy** and clarification that paragraphs 2 and 3 refer to the placebo-controlled trial
- Minor edits to section **2 Dosage and Administration** to clarify the description of the dosage for each indication
- Addition of an adverse reaction table for Trial 2 in subsection **6.1 Adverse Reactions/Clinical Trials Experience**
- Addition of a description of Trial 2 in subsection **14.2 Clinical Studies/Hepatic Encephalopathy**

APPROVAL & LABELING

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 enclosed agreed-upon labeling with minor editorial revisions listed below.

1. Subsection **2.1 Dosage for Travelers' Diarrhea** and **2.3 Dosage for Irritable Bowel Syndrome with Diarrhea**

    - Removal of the word "one" preceding the dosage to be consistent with subsection **2.2 Dosage for Hepatic Encephalopathy**. This revision is reflected in the enclosed labeling.

2. Subsection **14.2 Hepatic Encephalopathy,** Figure 3. Kaplan-Meier Event-Free Curves in Trial 2 (Time to First Breakthrough HE Event up to 6 Months of Treatment, Day 170) (All Randomized Subjects)

    - In the y-axis title, the word "Proportion" was misspelled. Correct this spelling error prior to submitting the labeling in SPL format.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated June 19, 2019, to IND 059133, cross-referenced to NDA 21361 on June 24, 2020, containing the final report for the following

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

postmarketing commitment listed in the March 24, 2010, approval letter under NDA 022554.

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.

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

We have reviewed your submission and conclude that the above commitment is fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the May 25, 2004, and the May 27, 2015, approval letters that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

[NOTE: The use of the term "new safety-related information" below includes new safety information (NSI) as described in section 505-1(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 355-1(b)) and other safety-related information unrelated to section 505(o)(4) of the FDCA.]

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- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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 Thao Vu, Safety Regulatory Project Manager, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
    - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JUDITH A RACOOSIN
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