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ESG

RESPONSE TO PREA NON-COMPLIANCE LETTER
DEFERRAL EXTENSION REQUESTED

Jessica J. Lee, MD, Director
Division of Gastroenterology (DG)
Office of Immunology and Inflammation
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 021361: XIFAXAN® (rifaximin) Tablets, 550 mg
Sequence 0127: Response to PREA Non-Compliance Letter
Deferral Extension Requested
Cross Reference
IND 071425
Sequence 0022

Dear Dr. Lee:

Reference is made to Salix Pharmaceuticals, Inc. (an affiliate of Bausch Health US, LLC) and NDA 021361, XIFAXAN® (rifaximin) Tablets, 200 mg and 550 mg for the treatment of travelers' diarrhea (TD); reduction in risk of overt hepatic encephalopathy (HE) recurrence; and the treatment of irritable bowel syndrome with diarrhea (IBS-D). Further reference is made to the Notice of PREA Non-Compliance Letter (Reference ID: 4856302) dated September 13, 2021.

Provided herein is the response to the PREA non-compliance letter as well as a deferral extension request. The deferral extension request is included in Section 1.11.4 of Module 1.

This submission is provided in electronic Common Technical Document (eCTD) format and is approximately 5 MB in size. The content of the submission has been verified to be free of viruses using the latest version of Carbon Black Defense. The submission is being provided via the

FDA's Electronic Submission Gateway (ESG). Please note that a letter of non-repudiation dated January 13, 2015 is on file with the Agency.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR § 314.430.

Should you have any questions or comments regarding this submission, please do not hesitate to contact me. Alternatively, you may contact Lee W. Evans, PhD, Vice President, Head of Global Regulatory Affairs at (908) 541-2179 or by email at lee.evans@bauschhealth.com.

Sincerely,

BAUSCH Health

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1.11.4 Multiple Module Information Amendment

With this amendment, the Sponsor respectfully requests a Deferral Extension. The reason for this request is due to a multitude of reasons listed below.

The new proposed date by which we expect to submit the assessment is December 2023.

1.11.4.1 DEFERRAL EXTENSION REQUESTED

Due to the COVID-19 global pandemic, study RFPK (b) (4) has not started enrollment. The global pandemic has caused delays in study start up activities.

FDA issued a general advice letter dated November 18, 2020 in response to final protocol RFPK (b) (4) submitted to IND 071425 July 13, 2020. The sponsor is evaluating FDA comments regarding the use of the adult dose and sparse PK sampling.

The sponsor has had difficulty gaining alignment with the CRO on study design.

Because the information in this request is substantively different from the first granted deferral extension request for PMR, we respectfully request a deferral extension.

1.11.4.1.1 Study Impact and Challenges

The items above have adversely impacted the start of study RFPK (b) (4). Enrollment for this study has been anticipated to be slow, and with the COVID-19 global pandemic still active, sites are anticipated to have difficulty enrolling pediatric subjects of this age.

Evaluation of the Agency's comments are ongoing. While the sponsor views these comments as favorable, administering the adult dose in the rifaximin (b) (4) tablets or other suitable formulation requires additional manufacturing of supplies (b) (4) The sparse PK sampling at baseline before dosing and at the time of maximum plasma drug concentration (C_{max}) previously determined in adults requires a change in study design and another protocol amendment.

The sponsor has had difficulty gaining alignment with CRO's on the study design and enrollment projections.

As referenced in Section 1.11.4, we expect to submit the assessment by December 2023. We propose deferral extension dates for the following:

Final Protocol Submission: December 2021
Study/Trial Completion: June 2023

Final Report Submission: December 2023