DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021200/S-015

SUPPLEMENT APPROVAL

Sloan Pharma S.a.r.l, Bertrange, Cham Branch
c/o US WorldMeds, LLC
ATTN: Rachael L. Gerlach, MSPH, Ph.D.,
Regulatory Affairs Specialist
4441 Springdale Rd
Louisville, KY 40241

Dear Dr. Gerlach:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 26, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zelnorm™ (tegaserod) oral tablets, 6mg.

This Prior Approval supplemental new drug application provides for revised labeling in the Indications and Usage section to limit the indication to treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation (IBS-C). Updated efficacy information was added to Clinical Studies. Safety information was revised in Contraindications, Warnings and Precautions, Adverse Reactions, and Patient Counseling Information. Corresponding revisions were made to the Medication Guide.

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.

We note that your March 15, 2019 submission includes structured product labeling (SPL) for your Prescribing Information and your March 21, 2019 submission includes SPL for your Medication Guide. We have not received final printed labeling (FPL) for your Prescribing Information and Medication Guide. You are responsible for assuring that the wording in the FPL is identical to that of the approved content of labeling in the 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), 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 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).

CARTON AND CONTAINER LABELING

We acknowledge your December 12, 2018, submission containing final printed carton labeling and your November 9, 2018 submission containing final printed container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the NDA itself was not withdrawn, marketing withdrawal alone did not affect the PREA requirements. You committed to honor the agreements, promises, and conditions contained in the NDA in your November 25, 2015 Acceptance of Ownership Letter, which included PREA requirements. The outstanding PREA requirements are clarified below.

We are waiving the pediatric study requirement for ages < 6 years because necessary studies are impossible or highly impracticable. This is because of the limited number of patients less than 6 years of age with IBS-C who require pharmacologic therapy and the complexities in studying this patient population.

We are deferring submission of your pediatric studies for ages 6 years to <18 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/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)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

3528-2 A double-blind, dose ranging and pharmacokinetic study in pediatric patients ages 6 years to less than 18 years to evaluate the safety and efficacy of oral Zelnorm (tegaserod) for 4 weeks as treatment for the relief of symptoms associated with IBS-C.

The timetable you submitted on March 7, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	October 2019
Final Protocol Submission:	April 2020
Study Completion:	April 2024
Final Report Submission:	October 2024

3528-3 A randomized, double-blind, placebo-controlled, parallel group, 12-week treatment study to assess the efficacy and safety of Zelnorm (tegaserod) in pediatric patients with IBS-C who are 6 years to less than 18 years of age.

The timetable you submitted on March 7, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	October 2024
Final Protocol Submission:	April 2025
Study Completion:	April 2027
Final Report Submission:	October 2027

3528-4 An active, comparator-controlled, safety and tolerability study for up to 24 weeks to assess the long-term safety of Zelnorm (tegaserod) in pediatric patients with IBS-C who are 6 years to less than 18 years of age and have completed a confirmatory efficacy and safety study with tegaserod.

The timetable you submitted on March 7, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	October 2024
Final Protocol Submission:	April 2025
Study/Trial Completion:	October 2027
Final Report Submission:	April 2028

Submit the protocol(s) to your IND 046264, 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 REQUIREMENTS UNDER 505(o)

Section 505(o)(3) 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.

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 an unexpected serious risk associated with the presence of tegaserod in human milk.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk associated with the presence of tegaserod in human milk.

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

3528-1 A lactation trial (milk only) in lactating women who have received therapeutic doses of Zelnorm (tegaserod) using a validated assay to assess concentrations of tegaserod in breast milk.

The timetable you submitted on March 7, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	July 2019
Final Protocol Submission:	January 2020
Trial Completion:	January 2021
Interim /Other:	February 2021
Final Report Submission:	November 2021

Submit the protocol(s) to your IND 046264, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) 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 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.

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 Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 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.

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 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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 Evangela Covert, Regulatory Project Manager, at 301-796-4075.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.P.H., M.D.
Deputy Director, Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Prescribing Information
Medication Guide
Carton and Container Labeling

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/

JOYCE A KORVICK
03/29/2019 09:50:20 AM