



NDA 208745/S-001

SUPPLEMENT APPROVAL

Synergy Pharmaceuticals, Inc.
Attn: Evelyn Jaeger
Vice President Regulatory Affairs & Clinical Quality Assurance
420 Lexington Avenue
Suite 2012
New York, NY 10170

Dear Ms. Jaeger:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 24, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trulance™ (plecanatide) oral tablets, 3mg.

This Prior Approval supplemental new drug application proposes a new indication for irritable bowel syndrome with constipation (IBS-C).

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 January 24, 2018, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (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 package insert 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 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

We acknowledge your January 19, 2018, 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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for ages birth to <6 years of age because necessary studies are impossible or highly impracticable. IBS is not generally described in patients younger than 6 years of age and is therefore not an appropriate indication for study in this age group.

We are deferring submission of your pediatric study(ies) for ages 6 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)(3)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

- 3304-1 Perform a double-blind, dose ranging study in pediatric patients ages 6 years to less than 18 years in order to evaluate the safety and efficacy of once daily oral Trulance (plecanatide) for 4 weeks as treatment of IBS-C. Patients will be

stratified by age group (6 years to 11 years and 12 years to less than 18 years of age).

Final Protocol Submission: 06/18
Study/Trial Completion: 03/20
Final Report Submission: 08/20

3304-2 Confirm the efficacy and safety of Trulance (plecanatide) treatment in pediatric patients with IBS-C who are 6 years to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12-week treatment study. Patients will be stratified by age (6 years to 11 years and 12 years to less than 18 years of age).

Final Protocol Submission: 09/20
Study/Trial Completion: 08/22
Final Report Submission: 11/22

3304-3 Assess the long-term safety of Trulance (plecanatide) once-daily treatment for chronic idiopathic constipation (CIC) or IBS-C in pediatric patients who are 6 years to less than 18 years of age and have completed the confirmatory efficacy and safety study with Trulance (plecanatide) by performing an open-label, active, comparator-controlled, safety and tolerability study for up to 24 weeks.

Final Protocol Submission: 02/21
Study/Trial Completion: 08/23
Final Report Submission: 11/23

Submit the protocol(s) to your IND 115118, 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 of development of immune-mediated reactions with the use of Trulance (plecanatide);
- to identify unexpected serious risks related to use of Trulance (plecanatide) in the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and theoretically lead to deficiency syndromes

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.

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

3304-4 Assess development of anti-drug antibody (ADA) responses in patient samples using the immunogenicity serum samples collected in the plecanatide studies (SP304203-04 and SP304203-05, and SP304203-06). Validated assays capable of sensitively and accurately detecting ADA responses, developed under PMR 3117-7, will be used. Evaluate the anti-drug antibody (ADA) rates, individual patient titers and the relationships between ADA status and the safety and efficacy of Trulance (plecanatide) in patients with IBS-C.

Final Report Submission: 04/2019

3304-5 Use the validated cross reactivity assays developed under PMR 3117-8 to test the ADA positive samples detected under PMR 3304-4. Evaluate the relationships between cross reactivity status and the safety and efficacy of Trulance (plecanatide) in patients with IBS-C.

Final Report Submission: 6/2020

3304-6 Use the validated neutralizing antibody assay developed under PMR 3117-9 to test the ADA positive samples detected under PMR 3304-4. Evaluate the relationships between neutralizing antibody status and the safety and efficacy of Trulance (plecanatide) in patients with IBS-C.

Final Report Submission: 08/2021

Submit the protocol(s) to your IND 115118, 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 package insert(s) 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 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>.

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