



NDA 208745

NDA APPROVAL

Synergy Pharmaceuticals Inc.
Attention: Evelyn Jaeger
Head of Regulatory Operations
420 Lexington Avenue, Suite 2012
New York, NY 10170

Dear Ms. Jaeger:

Please refer to your New Drug Application (NDA) dated January 29, 2016, received January 29, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trulance (plecanatide) tablets, 3 mg.

This new drug application provides for the use of Trulance (plecanatide) tablets for the treatment of chronic idiopathic constipation (CIC) in adults.

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 to Section 8.1 indicated in the enclosed labeling.

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, except with the revisions indicated, the enclosed labeling (text for the package insert and Medication Guide). 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on January 3, 2017, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208745.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Trulance was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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

We are waiving the pediatric studies requirement for ages birth to less than 2 years because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. In non-clinical studies of plecanatide, a guanlylate cyclase-C (GC-C) agonist, deaths due to dehydration occurred within 24 hours in young juvenile mice. This data and the literature regarding GC-C receptor ontogeny indicate that plecanatide would not be safe to administer to pediatric patients under 2 years of age.

We are deferring submission of your pediatric studies for ages 6 years to less than 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. We are deferring submission of your pediatric studies for ages 2 years to less than 6 years of age because this product is ready for approval for use in adults, and pediatric studies should be delayed in this age group until additional safety data from a study evaluating GC-C receptor ontogeny and the results of the clinical studies of plecanatide in older pediatric cohorts have been evaluated. In order to avoid severe diarrhea and its serious sequelae, nonclinical data and literature findings suggest special caution should be exercised in defining the initial plecanatide dose range for young pediatric patients.

Your deferred pediatric studies required by section 505B(a) of the 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 FDCA. These required studies are listed below.

- 3117-1. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 12 years to less than 18 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/31/15 (completed)
Study Completion: 12/18
Final Report Submission: 02/19

- 3117-2. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 12 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/18
Study Completion: 12/20
Final Report Submission: 02/21

- 3117-3. Confirm the efficacy and safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) 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.

Final Protocol Submission: 12/18
Study Completion: 12/21
Final Report Submission: 02/22

- 3117-4. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/20
Study Completion: 12/22
Final Report Submission: 02/23

- 3117-5. Confirm the efficacy and safety of Trulance (plecanatide) treatment in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission: 12/22
Study Completion: 12/25
Final Report Submission: 02/26

- 3117-6. Assess the long-term safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 18 years of age and have completed a confirmatory efficacy and safety study with plecanatide.

Final Protocol Submission: 02/17
Study Completion: 06/26
Final Report Submission: 08/26

Submit the protocols to your IND 74883, 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; or
- to assess a signal of a serious potential risk of a significant fluid shift into the intestine due to age-dependent expression of the target receptor (GC-C), leading to severe

dehydration and possibly death, in pediatric patients from birth to 6 years of age exposed to a GC-C receptor agonist.

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 these serious risks.

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

- 3117-7. Develop and validate a sensitive and precise assay for the detection of anti-plecanatide antibodies (ADA), including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling.

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/18

The final report should include screening, confirmation and titer assay validation reports and assay standard operating procedures (SOPs).

- 3117-8. Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin.

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/20

The final report should include assay validation reports and the assay standard operating procedures (SOPs).

- 3117-9. Develop and validate an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples taking Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/20

The final report should include assay validation report and the assay standard operating procedures (SOPs).

- 3117-10. A study to characterize guanylate cyclase-C (G-CC) mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients ages 0 to 6 years undergoing diagnostic gastrointestinal endoscopies as part of their medical care.

The timetable you submitted on October 13, 2016, states that you will conduct this study according to the following schedule:

| | |
|----------------------------|-------|
| Final Protocol Submission: | 12/17 |
| Study Completion: | 04/19 |
| Final Report Submission | 07/19 |

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will 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; or
- to identify an unexpected serious risk associated with the presence of plecanatide, or its active metabolite, in human breast milk.

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

- 3117-11. Assess development of anti-drug antibody (ADA) responses in patient samples using the immunogenicity serum samples collected in the plecanatide studies (SP304203-00 and SP304203-03 and SP304203-01). 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).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 04/19

- 3117-12. Use the validated cross reactivity assays developed under PMR 3117-8 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between cross reactivity status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 06/20

- 3117-13. Use the validated neutralizing antibody assay developed under PMR 3117-9 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between neutralizing antibody status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/21

- 3117-14. Perform a milk-only lactation trial in lactating women who have received multiple, once daily, doses of Trulance (plecanatide) therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order.

The timetable you submitted on October 13, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/17

Trial Completion: 06/18

Final Report Submission: 12/18

Submit the protocols to your IND 74883, 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 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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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>).

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. 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>.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

Content of Labeling
Medication Guide
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
01/19/2017