



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 guanylate 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).

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.