



NDA 211281

NDA APPROVAL

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
P.O. Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your new drug application (NDA) dated November 21, 2018, received November 21, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PIZENSY (lactitol) for oral solution.

We acknowledge receipt of your major amendment dated May 21, 2019, which extended the goal date by three months.

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

APPROVAL & LABELING

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 enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling:

- Removed a line of white space from the INDICATIONS AND USAGE section of Highlights
- Revised "> 3%" to "≥ 3%" in the ADVERSE REACTIONS section of Highlights
- Removed a line of white space between "FULL PRESCRIBING INFORMATION: CONTENTS" and "1 INDICATIONS AND USAGE" in the Table of Contents
- Revised "blood pressure increased" to "increased blood pressure" in the last sentence in ADVERSE REACTIONS, 6.1 Clinical Trials Experience.

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

FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) 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 *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the submitted carton and container labeling, except with the revisions to the container listed below, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 211281.**” Approval of this submission by FDA is not required before the labeling is used.

Container Labeling

- Enlarge the image of the cap in Step 2 to improve the readability of the “10 G” and arrow in the image.
- Enlarge the font size for the “20 G dose” and “10 G dose” labels on the images for Step 3.
- Bold the words “twice” and “once” in the instructions for Step 3.
- Revise the alignment and width of the text for the 20 gram dose in Step 3 so that the text is aligned under the corresponding image.

ADVISORY COMMITTEE

Your application for PIZENSY 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.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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.

We are waiving the pediatric study requirement for ages birth to less than 6 months because necessary studies are impossible or highly impracticable. This is because of the limited number of patients less than 6 months of age with functional constipation who require pharmacologic therapy and the complexities of studying this patient population.

We are deferring submission of your pediatric studies for ages 6 years to less than 17 years 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 6 months to less than 6 years for this application because pediatric studies should be delayed until additional nonclinical data have been collected. Juvenile toxicology studies to support clinical trials in patients who are 6 months to less than 6 years of age have not been completed.

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)(4)(C) of the FDCA. These required studies are listed below.

- 3754-1 A 12-week, randomized, double-blind, placebo-controlled, parallel-group study to assess the pharmacokinetics, efficacy, and safety of Pizensy (lactitol) for the treatment of functional constipation in pediatric patients 6 years to less than 17 years of age.

Final Protocol Submission: 09/2020

Trial Completion: 03/2022

Final Report Submission: 09/2022

- 3754-2 An oral (gavage) toxicity study with lactitol in juvenile rats from postnatal day (PND) 14 through PND 91 to support clinical trials in patients 6 months to less than 6 years of age.

Final Protocol Submission: 06/2020

Study Completion: 12/2020

Final Report Submission: 03/2021

3754-3 A 12-week, randomized, double-blind, placebo-controlled, parallel-group study to assess the pharmacokinetics, efficacy, and safety of Pizensy (lactitol) for the treatment of functional constipation in pediatric patients 6 months to less than 6 years of age.

Final Protocol Submission: 09/2020

Trial Completion: 06/2023

Final Report Submission: 12/2023

3754-4 A long-term extension study to assess the safety of Pizensy (lactitol) for the treatment of functional constipation in pediatric patients 6 months to less than 17 years of age who participated in trials for PMR 3754-1 or 3754-3.

Final Protocol Submission: 09/2020

Trial Completion: 12/2024

Final Report Submission: 06/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 118906, 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 a potential drug interaction that can lead to serious adverse

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

drug effects. An accurate assessment of an interaction is feasible only through *in vitro* mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

- 3754-5 *In vitro* studies to assess whether lactitol is a substrate, inhibitor, or inducer of metabolizing enzymes and transporters as outlined in the Guidance for Industry: *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (available at: <https://www.fda.gov/media/134582/download>). If *in vitro* studies suggest a potential for interaction, additional *in vivo* studies may be required.

The timetable you submitted on December 17, 2019 states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 05/2020

Final Protocol Submission: 08/2020

Study Completion: 05/2021

Final Report Submission: 11/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁴

Submit nonclinical and chemistry, manufacturing, and controls protocols and final report 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.

⁴ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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 Prescribing Information, Medication Guide, and Patient Package Insert (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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁵

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁶ Information and Instructions for completing the form can be found at FDA.gov.⁷ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁸

⁵ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁸ <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 FDA.gov.⁹

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

If you have any questions, contact Andrew Kelleher, Ph.D., Regulatory Project Manager, at (301) 796-9330 or email andrew.kelleher@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Victor Crentsil, M.D., M.H.S.
Acting Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and
Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Carton and Container Labeling

⁹ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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/

VICTOR CRENTSIL
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