CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210166Orig1s000

Trade Name:	Motegrity, 1 mg and 2 mg Oral Tablets
Generic or Established:	lanadelumab-flyo
Sponsor:	Shire Development LLC
Approval Date:	December 14, 2018
Indication:	For Chronic Idiopathic Constipation

CENTER FOR DRUG EVALUATION AND RESEARCH

210166Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 210166

NDA APPROVAL

Shire Development LLC
Attention: Sunil Kadam, Ph.D.
Senior Director, Global Regulatory Lead
300 Shire Way
Lexington, MA 02421-2101

Dear Dr. Kadam:

Please refer to your New Drug Application (NDA) dated December 21, 2017, received December 21, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Motegrity (prucalopride) 1 mg and 2 mg oral tablets.

This new drug application provides for the use of Motegrity (prucalopride) oral tablets for chronic idiopathic constipation.

APPROVAL & LABELING

We have completed our review of this application. 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 December 13, 2018 submission includes final printed labeling (FPL) for your Prescribing Information and your December 12, 2018 submission includes FPL for your Patient Package Insert. 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 Prescribing Information and Patient Package Insert) 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*, available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your July 31, 2018, submission containing final printed carton and 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.

We are waiving the pediatric studies requirement for ages birth to less than 6 months of age 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 in studying this patient population.

We are deferring submission of your pediatric studies for ages 6 months to less than 18 years 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 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. These required studies are listed below.

3529-1 Evaluate the pharmacokinetics, efficacy, and safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12-week treatment study.

Draft Protocol Submission:	03/2019
Final Protocol Submission:	07/2019
Study/Trial Completion:	03/2022
Final Report Submission:	09/2022

3529-2 Assess the long-term safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age and have completed a confirmatory efficacy and safety study with Motegrity (prucalopride) by performing an active comparator-controlled safety and tolerability study.

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Study/Trial Completion:	06/2023
Final Report Submission:	09/2023

Submit the protocol(s) to your IND 055078, 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 Federal Food, Drug, and Cosmetic Act 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 the long-term safety of prucalopride in women exposed during pregnancy, including assessing risks of pregnancy complications, and adverse effects on the developing fetus and neonate.

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 studies:

3529-3 A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Motegrity (prucalopride) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be

assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on December 7, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2019
Final Protocol Submission:	10/2019
Study Completion:	12/2025
Interim Report:	09/2021, 09/2022, 09/2023, 09/2024, 09/2025
Final Report Submission:	06/2026

3529-4 An additional pregnancy study that uses a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Motegrity (prucalopride) during pregnancy compared to an unexposed control population.

The timetable you submitted on December 7, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2019
Final Protocol Submission:	10/2019
Study Completion:	12/2025
Interim Report:	09/2021, 09/2022, 09/2023, 09/2024, 09/2025
Final Report Submission:	06/2026

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk associated with the presence of prucalopride, 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:

3529-5 Perform a milk only lactation trial in lactating women who have received therapeutic doses of Motegrity (prucalopride) using a validated assay to assess concentrations of prucalopride in breast milk and the effects on the breastfed infant.

The timetable you submitted on December 7, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2019
Final Protocol Submission:	12/2019
Study Completion:	04/2024
Interim Report:	09/2021, 09/2022, 09/2023
Final Report Submission:	08/2024

Submit clinical protocol(s) to your IND 055078 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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, 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 (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 Prescribing Information, 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 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.

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
  - Patient Package Insert
- 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/

VICTOR CRENTSIL
12/14/2018