DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209381

**NDA APPROVAL**

Norgine BV
Attention: Sangeeta Chavan Patil
Regulatory Affairs Project Manager
US agent for Norgine BV
B&H Consulting Services, Inc.
50 Division Street, Suite 206
Somerville, NJ 08876

Dear Sangeeta Chavan Patil:

Please refer to your New Drug Application (NDA) dated April 13, 2017, received April 13, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PLENVU (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution, 140 g, 48.11 g, 9 g, 7.54 g, 5.2 g, and 2.2 g, respectively.

We acknowledge receipt of your major amendment dated January 17, 2018, which extended the goal date by three months.

This new drug application provides for the use of PLENVU (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution, 140 g, 48.11 g, 9 g, 7.54 g, 5.2 g, and 2.2 g, respectively, for cleansing of the colon in preparation for colonoscopy 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 enclosed agreed-upon labeling text.

## 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, text for the Instructions for Use, and text for the 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

We acknowledge your April 30, 2018, submission containing final printed carton and container labels.

## MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Lawrence Allan
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building #22, Room: 5353
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code* 20903 *if shipping via United States Postal Service (USPS).*
*Use zip code* 20993 *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

## 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 deferring submission of your pediatric studies until July 2022, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under 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.

**3371-1** A study to evaluate safety, efficacy, tolerability, palatability and acceptability of PLENVU vs. an approved comparator in patients 12 to < 18 years of age. The study will include dose determination and PK evaluation.

Draft protocol submission: 06/2019

Final protocol submission: 08/2019
Trial completion: 09/2020
Final report submission: 03/2021

**3371-2** A study to evaluate safety, efficacy, tolerability, palatability and acceptability of PLENVU vs. an approved comparator in patients 2 to < 12 years of age. The study will include dose determination and PK evaluation.

Draft protocol submission: 09/2019
Final protocol submission: 11/2019
Trial completion: 12/2020
Final report submission: 06/2021

**3371-3** A study to evaluate safety, efficacy, tolerability of PLENVU vs. an approved comparator in patients 1 to < 2 years of age. The study will include dose determination and PK evaluation.

Draft protocol submission: 07/2020
Final protocol submission: 09/2020
Trial completion: 01/2022
Final report submission: 07/2022

Submit the protocol(s) to your IND 120089, 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 (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 assess an unexpected serious risk of systemically absorbed PEG3350 and possible presence of downstream metabolites.

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 to assess an unexpected signal of serious risk of systemically absorbed PEG3350 and possible presence of downstream metabolites.

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

> **3371-4** A phase 1 pharmacokinetic trial to adequately characterize the PK of PEG 3350 and its metabolites, diethylene glycol (DEG), and ethylene glycol (EG), and its secondary metabolites such as glycolic acid (GA), diglycolic acid (DGA), oxalic acid (OA) and hydroxyethoxyacetic acid (HEAA) in healthy subjects. Adequate bioanalytical assay methods with acceptable sensitivity should be developed for all analytes.

The timetable you submitted on April 18, 2018 states that you will conduct this trial according to the following schedule:

> Draft protocol submission: 9/2018
> Final protocol submission: 12/2018
> Trial completion: 09/2019
> Final report submission: 12/2019

Submit clinical protocol(s) to your IND 120089 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 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 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).

If you have any questions, call Lawrence Allan, Regulatory Project Manager, at (240) 402 – 2786.

Sincerely,

*{See appended electronic signature page}*

Lisa M. Soule, MD
Associate Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s): Content of Labeling, Carton and Container Labeling

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

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/s/

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LISA M SOULE
05/04/2018