# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209381Orig1s000

# OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** April 18, 2018

**To:** Lawrence Allan, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP Labeling Comments for PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)

**NDA**: 209381

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In response to Division of Gastroenterology and Inborn Errors Products' (DGIEP) consult request dated May 2, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution).

**PI and Medication Guide/IFU**: OPDP's comments on the proposed labeling are based on the draft PI, Medication Guide, and IFU received by electronic mail from DGIEP on March 15, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on March 27, 2018.

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 9, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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ADEWALE A ADELEYE
04/18/2018

**MEMORANDUM**

**REVIEW OF REVISED LABEL AND LABELING**

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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|---|---|
| **Date of This Memorandum:** | April 11, 2018 |
| **Requesting Office or Division:** | Division of Gastroenterology and Inborn Error Products (DGIEP) |
| **Application Type and Number:** | NDA 209381 |
| **Product Name and Strength:** | PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)<br>Dose 1 contains 100 grams of polyethylene glycol (PEG) 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF<br>Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 grams of potassium chloride, USP/NF<br>Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF. |
| **Submission date:** | April 9, 2018 |
| **Applicant/Sponsor Name:** | Norgine |
| **OSE RCM #:** | 2017-738-1 |
| **DMEPA Primary Reviewer:** | Sherly Abraham, RPh |
| **DMEPA Team Leader:** | Sarah K. Vee, Pharm.D. |

## 1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised carton labeling and container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous label and labeling review, OSE RCM #: 2017-738[a].

## 2 CONCLUSION

We find the revised container label and carton labeling acceptable and have no further recommendations at this time.

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[a]Abraham.S. Label and Labeling Review for Plenvu (NDA 209381). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Oct 24. 32 p. OSE RCM No.:2017-738

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/s/
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SHERLY ABRAHAM
04/12/2018

SARAH K VEE
04/12/2018

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | March 27, 2018 |
| To: | Donna Griebel, MD<br>Director<br>**Division of Gastroenterology and Inborn Error Products (DGIEP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Aman Sarai, BSN, RN<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Adewale Adeleye, Pharm.D., MBA<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU). |
| Drug Name (established name): | PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) |
| Dosage Form and Route: | for oral solution |
| Application Type/Number: | 209381 |
| Applicant: | Norgine |

## 1 INTRODUCTION

On April 13, 2017, Norgine resubmitted for the Agency's review a New Drug Application (NDA) 209381 for PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) for cleansing of the colon in preparation of a colonscopy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on May 2, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

## 2 MATERIAL REVIEWED

- Draft PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)MG and IFU received on April 13, 2017, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on March 15, 2018.
- Draft PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) Prescribing Information (PI) received on April 13, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 15, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level. In our review of the MG and IFU the target reading level is at or below an 8$^{th}$ grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The MG and IFU is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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AMANPREET K SARAI
03/27/2018

MARCIA B WILLIAMS
03/27/2018

ADEWALE A ADELEYE
03/27/2018

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | December 1, 2017 |
| **From** | Susan Leibenhaut, M.D., OSI/DCCE/GCPAB<br>Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB<br>Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB |
| **To** | Anil Nayyar, M.D., Medical Officer, DGIEP |
| **NDA** | 209381 |
| **Applicant** | Norgine, B.V. |
| **Drug** | PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride (NER1006) |
| **NME** | No |
| **Therapeutic Classification** | Cathartics and Laxatives |
| **Proposed Indication** | Cleansing of the colon in preparation for colonoscopy |
| **Consultation Request Date** | June 23, 2017 |
| **Summary Goal Date** | December 15, 2017 |
| **Action Goal Date** | February 13, 2018 |
| **PDUFA Date** | February 13, 2018 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA consisted of inspections of six clinical sites, three for each of two protocols, and of (b) (4), the contract research organization (CRO) responsible for the central reading(s) of the colonoscopy video to determine the primary endpoint, the Harefield Cleansing Scale. The data generated by these studies is acceptable in support of the application.

Five of the six CI sites and the CRO have a preliminary or final classification of NAI. For the MORA Study, Site 605 has a classification of VAI because records were damaged in a flood.

Inspections for the MORA Study at Sites 605 and 705 determined that there were data discrepancies in a total of four instances concerning whether and how much medication (test article) or required liquids the subject had taken. These discrepancies were due to lack of logic checks concerning data capture in the eCRF. The discrepancies in the data concerning test article administration seen at the two sites noted above were not seen at the third clinical site inspection for the MORA Study or at the clinical site inspections for the NOCT Study. There were no discrepancies concerning the efficacy endpoint. The sponsor was aware of this issue

prior to submission of the NDA and addressed this by submission of addendums to the safety reports for both studies.

The issues noted in the design of the eCRF have the potential to impact data collected at other study sites. The assessment of the appropriateness of the definition of the safety population is deferred to the review division.

# II. BACKGROUND

The sponsor submitted this NDA for NER1006 for the indication of use as a bowel cleansing preparation prior to colonoscopy. NER1006 is supplied in two formulations:

- macrogol 3350, sodium sulfate, and electrolytes to be reconstituted with water (up to 500 mL), intended for use as the first dose of the split prep: either the evening dose for the 2-day split-dosing regimen or as the first morning dose for the 1-day morning split-dosing regimen
- macrogol 3350, sodium ascorbate, ascorbic acid, and electrolytes to be reconstituted with water (up to 500 mL) is intended for use as the second dose of the split prep: either a morning dose for the 2-day split-dosing regimen or for the second morning dose for 1-day morning split-dosing regimen.

Current products marketed for bowel preparation include electrolyte balanced polyethylene glycol (PEG) bowel lavage solutions (e.g. GoLYTELY®, KLEAN-PREP®).

Norgine claims to have shown that administration of macrogol/sodium sulfate separately from the ascorbate components with an increased quantity of ascorbate components (ascorbic acid and ascorbate salt) results in a lower volume bowel preparation (1 L) required to provide a clean colon. The product is formulated to allow for a split dose, either evening/morning or two morning doses.

The sponsor conducted the two studies below to provide evidence that the product produced adequate cleansing of the colon. During the clinical trial, a colonoscopist at the site (i.e. local colonoscopist), blinded to treatment assignment, graded the cleansing of the colon using the Harefield Cleansing Scale. Video recordings of each colonoscopy were sent to (b) (4) the contract research organization (CRO) that provided the central reading(s). A central colonoscopist (first reader) performed an independent assessment of the segmental cleansing using the HCS, and the HCS grade was automatically computed from the scores entered in the e-CRF. If the two assessments (local colonoscopist and central reader) of overall bowel cleansing efficacy success or failure matched, the first reader's results were used for the primary and secondary endpoint analysis. If the two assessments differed, a second central colonoscopist (second reader) performed an independent assessment of the segmental cleansing using the HCS, and the results of this assessment were used for the primary and secondary endpoint analysis.

Drug:
PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride (NER1006)

Study– Protocol number and title for all studies that were inspected:

1. NER1006-02/2014 (MORA) entitled "A Multicenter Randomized Parallel Group Phase III Study Comparing the Bowel Cleansing Efficacy, Safety and Tolerability of NER1006 (a Low Volume Bowel Cleansing Solution) versus MOVIPREP® using a 2-Day Split-Dosing and 1-Day Morning Split-Dosing Regimens in Adults"

   Number of subjects: 849 subjects
   Number of sites: 29
   Number of countries where subjects were enrolled: six
   Dates that study was conducted: October 2014 to August 2015
   Efficacy endpoint: bowel cleansing using the Harefield Cleansing Scale (HCS)

2. NER1006-01/2014 (NOCT) entitled "A Multicenter Randomized Parallel Group Phase III Study Comparing the Bowel Cleansing Efficacy, Safety and Tolerability of NER1006 (a Low Volume Bowel Cleansing Solution) versus a Trisulfate Bowel Cleansing Solution using a 2-Day Split-Dosing Regimen in Adults"

   Number of subjects: 621 subjects
   Number of sites: 12
   Number of countries where subjects were enrolled: U.S. only
   Dates that study was conducted: September 2014 to June 2015
   Efficacy endpoint: bowel cleansing using the Harefield Cleansing Scale (HCS)

# III. RESULTS (by site):

| Name and type of inspected entity/Address | Protocol # /Site # / # of Subjects | Inspection Dates | Classification |
|---|---|---|---|
| CI: Marco Antonio Álvarez González, M.D.<br>Hospital del Mar<br>Passeig Maritim 25-29<br>Barcelona, Spain | NER1006-02/2014 (MORA)<br>Site 705<br>113 Subjects | September 12 to 15, 2017 | NAI |
| CI: Maria Wisniewska-Jarosinska, M.D., Ph.D.<br>Ul. Pilota Stanislawa Wigury 19<br>Lodz, Lodzkie, 90-302, Poland | NER1006-02/2014 (MORA)<br>Site 605<br>98 Subjects | September 18 to 20, 2017 | VAI |
| CI: Peter Uebel, M.D.<br>Praxis fur Innere Medizin und Gastroenterologie und Allgemeinmedizin Ludwigshafen Hospital<br>Leininger Str. 51-53, Ludwigshafen am Rhein, 45136 Germany | NER1006-02/2014 (MORA)<br>Site 402<br>102 Subjects | October 23 to 27, 2017 | *NAI |
| CI: Michael P. DeMicco, M.D.<br>Anaheim Clinical Trials, Suite 303<br>1211 West La Palma Avenue<br>Anaheim, CA 92801 | NER1006-01/2014 (NOCT)<br>Site 102<br>142 subjects | October 12 to 17, 2017 | NAI |
| CI: Joseph B. Henderson, M.D.<br>Cumberland Research Associates<br>2109 Valleygate Drive, Ste. 102<br>Fayetteville, NC 208304 | NER1006-01/2014 (NOCT)<br>Site 109<br>96 subjects | November 7 to 15, 2017 | *NAI |
| CI: Kenneth Lee Kelln, M.D.<br>Advanced Research Institute<br>5896 South Ridgeline Drive, Ste. C<br>South Ogden, UT 84405 | NER1006-01/2014 (NOCT)<br>Site 110<br>125 subjects | October 25 to November 2, 2017 | NAI |
| CRO:<br>(b) (4) | NER1006-01/2014 (NOCT)<br><br>NER1006-02/2014 (MORA) | October 15 to 24, 2017 | *NAI |

Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Marco Antonio Álvarez González, M.D.
   Hospital del Mar, Passeig Maritim 25-29, Barcelona, Spain

At this site, 113 subjects were screened and randomized, and 109 subjects completed the study. There were no deaths or serious adverse events (SAEs) reported. No subjects were discontinued from the study other than for personal reasons. An audit of 59 subjects' records was conducted. This included review of informed consent, inclusion/exclusion criteria, protocol adherence, adverse events, concomitant medications, and a 100% data audit against the primary efficacy endpoint of colon cleansing and the subject compliance diaries. No Form FDA-483 was issued.

Inspection revealed data discrepancies in three instances detailed below concerning whether and how much medication or required liquids the subject had taken.

1. Subject (b) (6) (randomized to Moviprep) reported taking only half of the required liquids, but this was entered into the eCRF as "all" because the eCRF did not have an entry for half of liquids taken.
2. Subject (b) (6) (randomized to Moviprep) completed a diary, but this was not entered into the eCRF due to a deficiency with the eCRF that did not flag the omission for additional query. The line listing states missing even though a value should have been entered, so this subject was excluded from the safety set even though they took medication.
3. Subject (b) (6) (randomized to NER1006 1 Day morning split dose) reported not taking the second dose and this was entered as "missing" instead of "none." The site could not enter "none" in the eCRF because it was not an option available in the configuration of the eCRF. In the audit trail, the site responded to the missing data queries and accurately reported that the Subject did not take the dose. However, the eCRF did not have an option to enter a dose as not taken. Therefore, it was reported by the sponsor as "missing" which is inaccurate.

*Reviewer comments:*
*The deficiencies noted above were the result of the design of the eCRF, so this deficiency may have impacted data collected at other study sites; however, this finding was noted only at two sites, this site and at Site 605 as noted below. While the inspection was ongoing, the sponsor representative notified the FDA field investigator that Norgine had become aware of the issues noted above after the study had been conducted. (Note that the issue with Item #1 concerns the amount of liquid ingested, not of test article ingested.)*

*In the original submission of the NDA to the FDA in September 2016, the review division noted that missing data was not handled appropriately and that the sponsor had defined the Safety Set as "All randomized patients who received at least one dose of randomized investigational product during the course of the study". The sponsor withdrew the NDA in November 2016 because of this issue.*

*In the resubmission of the NDA in April 2017, the sponsor submitted an addendum to the Clinical Study Report with results of a post ad hoc safety analysis which included a different definition of the safety population. This second safety set (SAF2) included all randomized patients for whom it could not be ruled out from the diary and drug reconciliation record that they did not take the study drug at least once.*

The study appears to have been conducted adequately at this site. The data can be considered reliable in support of the application. The assessment of the appropriateness of the definition of the safety population is deferred to the review division.

2. Maria Wisniewska-Jarosinska, M.D., Ph.D.
   Ul. Pilota Stanislawa Wigury 19. Lodz, Lodzkie, 90-302, Poland

At this site, 99 subjects were screened, 98 subjects were randomized, and 90 subjects completed the study. There were no deaths or SAEs reported. An audit of 53 subjects' records was conducted. Inspection included verification of informed consent documents, eligibility criteria, concomitant medications, diary entries (compliance), adverse events, (AEs) and efficacy data (Harefield scores). The efficacy data were verified, and there was no evidence of under-reporting of AEs.

A Form FDA 483 was issued for inadequate records due to flooding at the site having destroyed parts of subject records. These items were primarily laboratory reports and subject diaries where the subject recorded intake of test article. The destruction did not include the colonoscopy records. Another issue noted at this site was the study wide issue concerning inadequate design and functionality of the eCRF resulting in missing data concerning whether and how much medication a subject had taken. This issue is described in detail in the report of the inspection of Dr. Álvarez-González (summarized above) in Spain. At this site, the issue was noted in Subject (b) (6), randomized to MOVIPREP®. The source records state that the subject took one dose of the test article and then withdrew from the study. The line listings state that the subject did not take test article. The sponsor addressed this study-wide issue in an addendum to the study report.

Dr. Wisniewska-Jarosinska adequately responded to the inspectional findings in a letter dated September 20, 2017. The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. Peter Uebel, M.D.
   Praxis fur Innere Medizin und Gastroenterologie und Allgemeinmedizin
   Ludwigshafen Hospital, Ludwigshafen am Rhein, 45136 Germany

Note: Observations below for this clinical investigator (CI) inspection are based on

communications with the FDA field investigator and on records and notes exchanged during these communications. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site, 102 subjects were screened and a total of 101 subjects were randomized, and completed the study. There were no deaths or SAEs reported. No subjects were discontinued from the study other than for personal reasons. An audit of 41 subjects' records was conducted. This included review of informed consent, inclusion/exclusion criteria, protocol adherence, adverse events, concomitant medications, and a 100% data audit against the primary efficacy endpoint of colon cleansing and the subject compliance diaries. There was no Form FDA-483 issued.

The study appears to have been conducted adequately at this site.

4. Michael P. DeMicco, M.D.
   Anaheim Clinical Trials, Anaheim, CA 92801

This inspection was performed as a data audit for NDA 209381. At this site, 157 subjects were screened, 142 subjects were randomized, and 121 subjects completed the study. There were no deaths or SAEs reported. Source documentation for reasons for discontinuation were compared with the line listings and verified. A review of 70 subject records was conducted of informed consent documents, eligibility criteria, concomitant medications, diary entries (compliance), adverse events, (AEs) and efficacy data (Harefield scores). No discrepancies were noted and there was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

5. Joseph B. Henderson, M.D.
   Cumberland Research Associates, 2109 Valleygate Drive, Fayetteville, NC 208304

Note: Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

This inspection was performed as a data audit for NDA 209381. At this site, 103 subjects were screened, 96 subjects were randomized, and 75 subjects completed the study. There were no deaths or SAEs reported. Source documentation for reasons for discontinuation were compared with the line listings and verified. A review of 43 subject records was conducted of informed consent documents, eligibility criteria, concomitant medications, diary entries (compliance), adverse events, (AEs) and efficacy data (Harefield scores). No discrepancies were noted and there was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

6. Kenneth Lee Kelln, M.D.
Advanced Research Institute, South Ogden, UT 84405

This inspection was performed as a data audit for NDA 209381. At this site, 135 subjects were screened and 128 subjects were randomized, and 104 subjects completed the study. There were no deaths or SAEs reported. Source documentation for reasons for discontinuation were compared with the line listings and verified. A review of 39 subject records was conducted of informed consent documents, eligibility criteria, concomitant medications, diary entries (compliance), adverse events, (AEs) and efficacy data (Harefield scores). No discrepancies were noted and there was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

7. (b) (4)

Note: Observations below for this CRO inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

The primary focus of this inspection was the review and evaluation of the CRO's SOPs for site and central reader blinding, central reader training, and processing and review of procedure videos by the site and central reviewers. Comparison of the subject eCRF data with the relevant data listing for the Harefield Cleansing Scale and bowel cleansing success or failure revealed no discrepancies SOPs and Work Instructions were in effect and were reviewed for site reader and central reader blinding and training. SOPs and work instructions were also in place and reviewed for data management, database, image processing, and project management.

The primary efficacy endpoint data, Harefield Cleansing Scale and overall bowel cleansing were verifiable through comparison of subjects eCRF data maintained by the CRO for select subjects with the Harefield Cleansing Scale data contained in the data listing for site reader, the central reader (first reader) and were applicable the second reader. If the overall adjudication of the procedure was not in agreement between the site reader and the first central reader, a second reader reviewed the procedure video and the overall result of success or failure was based upon the second reader's assessment. Total subject records reviewed for both the NOCT and MORA studies for those clinical sites listed in the inspection assignment (Sites 102,

109, 110, 402, 605, and 705) was 143 of the total 676 total cases from the selected clinical site.

The studies appear to have been conducted adequately by the CRO and the data is considered reliable in support of the indication.

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Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
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cc: Central Doc. Rm.
Review Division /Division Director/Donna Griebel
Review Division /Medical Team Leader/Tara Altepeter
Review Division /Project Manager/Lawrence Allen
Review Division/Medical Officer/Anil Nayyar
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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SUSAN LEIBENHAUT
12/04/2017

SUSAN D THOMPSON
12/04/2017

KASSA AYALEW
12/04/2017

**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

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| **Date of This Review:** | October 24, 2017 |
| **Requesting Office or Division:** | Division of Gastrointestinal and Inborn Errors Products (DGIEP) |
| **Application Type and Number:** | NDA 209381 |
| **Product Name and Strength:** | PLENVU (polyethylene glycol (PEG), sodium sulfate, sodium ascorbate, ascorbic acid, sodium chloride and potassium chloride) for Oral Solution<br>Total strength: 140 g polyethylene glycol (PEG), 48.11 g of sodium ascorbate, 9g of sodium sulfate, 7.54g of ascorbic acid, 5.2 g of sodium chloride and 2.2 g of potassium chloride<br>Dose 1 contains 100 grams of polyethylene glycol (PEG) 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF.<br>Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 grams of potassium chloride, USP/NF.<br>Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF. |
| **Product Type:** | Multi-ingredient product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Norgine |
| **Submission Dates:** | April 13, 2017<br>July 14, 2017 |
| **OSE RCM #:** | 2017-738 |
| **DMEPA Primary Reviewer:** | Sherly Abraham, R.Ph. |
| **DMEPA Team Leader:** | Sarah K. Vee, Pharm.D. |

## 1 REASON FOR REVIEW

This review evaluates the labels and labeling for NDA 209381, PLENVU (PEG 3350, sodium ascorbate, sodium chloride, ascorbic acid, sodium chloride and potassium chloride), resubmitted on April 13, 2017. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information (PI), pouch labels, carton labeling and Instructions for Use (IFU) for any areas of vulnerability that may lead to medication errors.

### 1.1 REGULATORY HISTORY

NDA 209381 was originally submitted on September 16, 2016, but was withdrawn by the Applicant on December 1, 2016. The Applicant resubmitted the NDA on April 13, 2017.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

**Table 1. Materials Considered for this Label and Labeling Review**

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B-N/A |
| Human Factors Study | C-N/A |
| ISMP Newsletters | D-N/A |
| FDA Adverse Event Reporting System (FAERS)* | E-N/A |
| Other | F-N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Norgine submitted PLENVU (PEG 3350, sodium ascorbate, sodium chloride, ascorbic acid, sodium chloride and potassium chloride) indicated for cleansing of the colon in preparation for colonoscopy in adults.

We identified areas in the PI, pouch labels, carton labeling and IFU that can be improved to increase the clarity of information to promote the safe use of the product. We note that the PI only has the individual pouch strengths but missing the total strength. This is inconsistent with the pouch labels and carton labeling. We defer the decision to add the total strength presentation on the PI to OPQ (Office of Pharmaceutical Quality). We also note that Patient

Counseling section and IFU can be further clarified with adding “three pouches” in parenthesis for “both doses” or “two doses” and “two pouches” in parenthesis for Dose 2 to avoid confusion since there are three packets in the carton and two packets for Dose 2. We provide letter-ready recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, pouch labels, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 and 4.2 below.

### 4.1 RECOMMENDATIONS FOR DIVISION

#### A. FULL PRESCRIBING INFORMATION: SECTION 2 DOSAGE AND ADMINISTRATION

1. Consider replacing the abbreviation “fl oz” with “fluid ounces” to prevent misinterpretation and confusion.

2. We recommend adding the stirring time (i.e., 8 minutes) to the preparation instructions to emphasize the longer than usual time to dissolve the product. For example, “Mix for up to approximately 8 minutes to completely dissolve the contents into the water”.

3. We recommend using the numbering format instead of bulleting format for dose 2 preparations of two-day split and one-day morning regimen so the end user can follow the steps in a sequential manner.

#### D. Instructions for Use (IFU)

1. Change “(b) (4)” to “12 hours” under “morning only dosing schedule” to be consistent with the PI.

2. Consider replacing the abbreviation “fl oz” with “fluid ounces” to prevent misinterpretation and confusion.

3. Add the stirring time (8 minutes) to instructions step 1 and step 3 to avoid overlooking this important instruction. This is an unusual time and should be emphasized. Additional statement under “note:” can be deleted.

### 4.2 RECOMMENDATIONS FOR NORGINE

We recommend the following be implemented prior to approval of this NDA:

**A. Pouch Labels and Carton Labeling:**

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

2. Present the established names with a parenthesis on both ends and each name in lower case. For example,

PLENVU
(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, 2.2g

3. Add a statement on the Principal Display Panel (PDP), "Reconstitute and dilute in water prior to use" to avoid the usage of this product without reconstitution and dilution.

4. Add the statement on the PDP "Dispense the enclosed Medication Guide to each patient" or a similar statement in accordance with 21 CFR 208.24(d).

5. Add the lot number and the expiration date on all labels.

6. Ensure that all instructions and storage information is consistent with the final prescribing information and Instructions for Use.

**B. Pouch Labels Only:**

1. As currently presented, the NDC number is denoted by a placeholder (XXXXX-XXXX-XX). Revise the placeholder to display the actual NDC number.

**C. Tertiary Carton Labeling Only:**

1. Replace the term (b) (4) with "mixing container" on the PDP of the labeling to be consistent with the prescribing information.

**D. Secondary Carton Labeling and Tertiary Carton Labeling Only:**

1. As currently displayed, the statement, (b) (4) might cause confusion since there are three packets inside the carton. Revise and bold the statement to "All of Dose 1 (one pouch) and Dose 2 (two pouches) must be consumed."

2. Add a net quantity statement on the PDP in accordance with 21 CFR 201.51 and away from the product strength and have less prominence.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for PLENVU that Norgine submitted on April 13, 2017 and July 14, 2017

| **Table 1. Relevant Product Information for PLENVU** | |
|---|---|
| **Product:** | PLENVU |
| **Initial Approval Date:** | N/A |
| **Active Ingredients** | polyethylene glycol (PEG) 3350, sodium ascorbate, sodium chloride, ascorbic acid, sodium chloride and potassium chloride |
| **Indication** | PLENVU is indicated for cleansing of the colon in preparation for colonoscopy in adults |
| **Route of Administration** | oral |
| **Dosage Form:** | solution |
| **Strength:** | Total strength: 140 g polyethylene glycol (PEG), 48.11 g of sodium ascorbate, 9g of sodium sulfate, 7.54g of ascorbic acid, 5.2 g of sodium chloride and 2.2 g of potassium chloride<br>Dose 1 contains 100 grams of polyethylene glycol (PEG) 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF.<br>Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 grams of potassium chloride, USP/NF.<br>Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF. |
| **Dose and Frequency** | Two-day split regimen: Dose 1 the evening before the colonoscopy (approximately 4pm to 8pm) and Dose 2 the next morning, approximately 12 hours after the start of Dose 1.<br>One-day morning regimen: Dose 1 the morning of the colonoscopy (approx. 3am to 7am) and Dose 2 approx. 2 hours after the start of Dose 1. |

| | |
|---|---|
| **How Supplied:** | PLENVU is supplied as a white to yellow powder for oral solution.<br><br>Each carton contains a disposable mixing container for reconstitution of PLENVU and three pouches labeled Dose 1, Dose 2 Pouch A and Dose 2 Pouch B. |
| **Storage:** | Store carton at room temperature, between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59°F to 86°F (15°C to 30°C). The carton may be stored in a refrigerator. |
| **Container closure:** | N/A |

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following PLENVU labels and labeling submitted by Norgine on April 13, 2017 and July 14, 2017

- Pouch labels
- Carton labeling
- Prescribing Information (Image not shown)
- Instructions for Use (Image not shown)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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SHERLY ABRAHAM
10/24/2017

SARAH K VEE
10/26/2017