CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209381Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: As of this review, this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6).

NDA 209381
OPQ Review #1

Drug Name/Dosage Form	PLENVU (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution
Strength	• 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. • 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. • Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF.
Route of Administration	Oral solution
Rx/OTC Dispensed	Rx
Applicant	Norgine B.V., The Netherlands
US agent, if applicable	B & H Consulting Services, Inc.; Somerville, NJ

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	9/16/2016	OPQ
Amendment	4/13/2017	ONDP/DNDAPI/ONDP/OPF
Amendment	7/14/2017	ONDP
Amendment	7/27/2017	ONDP/DNDAPI
Amendment	10/06/2017	ONDP/DNDAPI/ONDP/OPF
Amendment	11/13/2017	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika Englund	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Sarah Ibrahim	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Kejun Cheng	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Kejun Cheng	CDER/OPQ/OPF/ DPAIII/PABVIII
Facility	Xiaohui (Sherry) Shen	CDER/OPQ/OPF/DIA/IABIII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
Environmental Analysis (EA)	Sarah Ibrahim	CDER/OPQ/ONDP/ DNDPII/NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4) Polyethylene Glycol 3350	Active	Adequate (Reviewed by Erika E. Englund, Ph.D. on 11/16/2017)	LOA: 05/23/2016
	Type II		Potassium Chloride	Active	Adequate (NAI 08/30/2016)	LOA: 09/05/2016
	Type II		Sodium Chloride	Active	Adequate (NAI 08/05/2016 by Wei Song, Ph.D.)	LOA: 07/05/2017
	Type II		Sodium Sulfate Anhydrous	Active	Adequate (Reviewed by Erika E. Englund, Ph.D. on 09/08/2017)	LOA: 05/09/2016
	Type II		Ascorbic Acid	Active	Adequate (Reviewed by Erika E. Englund, Ph.D. on 12/22/2017)	LOA: 08/30/2016
	Type II		Sodium Ascorbate	Active	Adequate (Reviewed by Erika E. Englund, Ph.D. on 12/22/2017)	LOA: 02/17/2017

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	120089	Polyethylene Glycol 3350, Ascorbic Acid, Sodium Ascorbate, Sodium Chloride, Sodium Sulfate, and Potassium Chloride, for oral solution

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application as of this review.

The label/labeling issues have ***not*** been satisfactorily resolved.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per 21 CFR 314.125(b)(6).

II. Summary of Quality Assessments

A. Product Overview

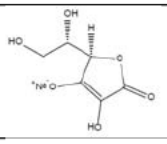
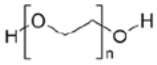
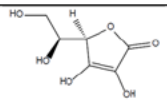
Plenvu (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for solution is an osmotic laxative. It is supplied as a powder in three pouches. Pouch 1 is for Dose 1, Pouch A and Pouch B are for Dose 2. Plenvu is dissolved in water for oral administration.

Plenvu contains 140 g of polyethylene glycol 3350, 9 g of sodium sulfate, 5.2 g of sodium chloride, 2.2 g of potassium chloride, 48.1 g of sodium ascorbate and 7.5 g of ascorbic acid. It also contains the following inactive ingredients: sucralose, aspartame, encapsulated citric acid, mango flavor and fruit punch flavor.

Proposed Indication(s) including Intended Patient Population	PLENVU® is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.
Duration of Treatment	Administered only once prior to colonoscopy procedure
Maximum Daily Dose	Two-day split dosing regimen or one-day morning dosing regimen. For oral solution: First dose: one pouch labeled Dose 1; Second dose: two pouches labeled Dose 2 Pouch A and Dose 2 Pouch B. • 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. • 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. (**Error! Reference source not found.**) • Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF
Alternative Methods of Administration	**N/A**

B. Quality Assessment Overview

Drug Substances:
The drug substances in Plenvu are the following: polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride. All drug substances are USP/NF grade. The complete CMC information is provided in the DMFs from the manufacturers. The following DMFs were reviewed and deemed adequate.

DMF	Chemical Name	Structure	DMF Holder	Status
(b) (4)	Sodium Ascorbate		(b) (4)	Adequate (Reviewed by Erika E. Englund, Ph.D. on 12/22/2017)
	Polyethylene Glycol 3350			Adequate (Reviewed by Erika E. Englund, Ph.D. on 11/16/2017)
	Potassium Chloride	KCl		Adequate (NAI 08/30/2016)
	Ascorbic Acid			Adequate (Reviewed by Erika E. Englund, Ph.D. on 12/22/2017)
	Sodium Chloride	NaCl		Adequate (NAI 08/05/2016 by Wei Song, Ph.D.)
	Sodium Sulfate	Na_2SO_4		Adequate (Reviewed by Erika E. Englund, Ph.D. on 09/08/2017)

The Office of Process and Facilities (OPF) reviewer, Dr. Xiaohui (Sherry) Shen has made an "Adequate" recommendation for manufacturing and testing facilities of all drug substances (See the **Facilities** review).

All drug substances in Plenvu are controlled to conform to the requirements (specification) to produce Plenvu for solution.

Drug Product:
Plenvu for oral solution is supplied in three pouches containing white to yellow powder for reconstitution. Plenvu contains 140 g of polyethylene glycol 3350, 9 g of sodium sulfate, 5.2 g of sodium chloride, 2.2 g of potassium chloride, 48.1 g of sodium ascorbate and 7.5 g of ascorbic acid. It also contains the following inactive ingredients: sucralose, aspartame, encapsulated citric acid, mango flavor and fruit punch flavor. Plenvu does not contain any preservatives or antioxidants in its formulation.

Plenvu is manufactured by Norgine Limited, Hengoed, UK. The manufacturing process is comprised of (b) (4) All manufacturing procedures and operations are performed in accordance with current Good Manufacturing Practices described in 21 CFR Part 211. The drug product

manufacturing process was reviewed by Dr. Kejun Cheng and was deemed acceptable. (See **Process** review)

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, assay, impurities, water content, content uniformity, and microbial limits. For assay and impurities determinations, the applicant developed and used non-compendial, validated in-house methods. Based on long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 24-month of expiration dating period when stored between 20ºC to 25ºC in the proposed container closure system is granted. The reconstituted solution should be used within 6 hours. (See the **Drug Product** review by Dr. Sarah Ibrahim).

The Office of Process and Facilities (OPF) reviewer, Dr. Xiaohui (Sherry) Shen, has made an "Adequate" recommendation for the drug substances and drug product manufacturing and testing facilities involved in this NDA. (See the **Facility** review).

An environmental impact analysis assessment with calculation of estimated entry into aquatic environment, less than 1 ppb, was provided with a statement that no extraordinary circumstances exist. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 was deemed acceptable.

The labels and labeling issues are ***not*** satisfactorily resolved from the CMC perspective according to the labeling reviewer, Dr. Sarah Ibrahim. Therefore, this application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the OPQ perspective until the deficiencies listed below are satisfactorily resolved. (See the **Labeling** review).

C. Lifecycle Management Consideration (NDA only)

(b) (4)

The Office of Process and Facilities recommended routine surveillance inspections per Office of Surveillance work plan for the facilities involved in this NDA.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies:

The following labeling comments should be resolved with the applicant.

A. <u>Regarding PI</u>

a) Highlight Section

- The title should be revised to;

  "Plenvu (PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution"

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- The Trade name should be included.

#11: Description

- The established name should be revised to;

  "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution"

- Each active ingredient; PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid should be listed with their chemical name, chemical formulae, molecular weight, and structure.

#16: How Supplied/Storage and Handling

- "Plenvu is supplied as a white to yellow powder" needs to be revised to

  "Plenvu is supplied as a white to yellow powder to be reconstituted for oral solution: One pouch labeled Dose 1; Two pouches labeled A and B for Dose 2
  •• The pouch for 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; (b) (4) the following excipients: sucralose, NF (b) (4); encapsulated citric acid (b) (4); and mango flavoring (3).
  •• Pouch A for Dose 2 contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF; (b) (4), the following excipients: aspartame, NF (b) (4); and fruit punch flavoring (3).
  •• Pouch B for Dose 2 contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF (3).

B. Regarding Container/Carton Labels:

a) In immediate container label,

- Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution"
- Lot number and expiry date should be displayed.

b) Secondary carton

- Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution"
- The font size of established name should be at least 50% of the tradename.
- The font color must be prominent as much as the tradename.
- Lot number and expiry date should be displayed.

c) Tertiary carton

- Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for oral solution"
- The font size of established name should be at least 50% of the tradename.
- The font color must be prominent as much as the tradename.
- Lot number and expiry date should be displayed.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
January 05, 2018

Hitesh N. Shroff -S

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

Plenvu [redacted] (b) (4) (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride)

2) DOSAGE FORMS AND STRENGTHS

[redacted] (b) (4) for oral solution: First dose: one pouch labeled Dose 1; Second dose: two pouches labeled Dose 2 Pouch A and B.

• 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; [redacted] (b) (4) .

• Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF; [redacted] (b) (4) (3).

• Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF (3).

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Plenvu (b) (4) (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride)	Proprietary name is proposed and is acceptable. The title is not acceptable. It should be revised to "Plenvu (polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) **Not Satisfactory.**
Dosage form, route of administration	(b) (4) **for oral solution**	The dosage form, (b) (4) for oral solution, is described inadequately and should be revised to "Powder to be reconstituted for oral solution" Route of administration, oral, is presented correctly. **Not Satisfactory.**
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))	(b) (4) for oral solution: First dose: one pouch labeled Dose 1; Second dose: two pouches labeled Dose 2 Pouch A and B. •• 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, (b) (4) •• Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF; (b) (4) •• Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF (3).	The dosage form, powder for oral solution, should be revised to "Powder to be reconstituted for oral solution". The strength for each pouch for each Dose is described correctly. **Not Satisfactory.**
Whether the drug product is scored		

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

Powder for [redacted] (b) (4): First dose: one pouch labeled Dose 1; Second dose: two pouches labeled Dose 2 Pouch A and Dose 2 Pouch B.

•• Dose 1 contains 100 grams of PEG 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF; [redacted] (b) (4)

•• Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF; [redacted] (b) (4).

•• Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Powder for (b) (4)	Proprietary name should be included. Dosage form should be revised to "Powder to be reconstituted for oral solution" **Not Satisfactory.**
Strengths: in metric system	•• Dose 1 contains 100 grams of PEG 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride •• Dose 2 Pouch A contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF •• Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF.	The strength is presented correctly for each Dose and for each pouch. **Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)	NA	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Powder for oral solution	The description is correctly expressed. **Satisfactory.**

2) #11: DESCRIPTION

Plenvu (PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) is an osmotic laxative consisting of three pouches (one for Dose 1, one for Dose 2 Pouch A and one for Dose 2 Pouch B) containing white to yellow powder for reconstitution.

Dose 1 contains 100 grams of PEG 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF; (b) (4) the following excipients: sucralose, NF (b) (4); encapsulated citric acid (b) (4); and mango flavoring. When Dose 1 is dissolved in water to a volume of 16 fl. oz., Plenvu Dose 1 (PEG 3350, sodium sulfate, sodium chloride, potassium chloride) is an oral solution having a mango (b) (4).

Each Dose 2 Pouch A contains 40 grams of polyethylene glycol (PEG) 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 grams of potassium chloride, USP/NF; (b) (4) the following excipients: aspartame, NF (b) (4) and fruit punch flavoring.

Each Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF and 7.54 grams of ascorbic acid, USP/NF.

When Dose 2 Pouch A and Dose 2 Pouch B are dissolved together in water to a volume of 16 fl. oz., Plenvu Dose 2 (sodium ascorbate, PEG 3350, ascorbic acid, sodium chloride and potassium chloride) is an oral solution having a fruit punch (b) (4).

The entire, reconstituted, 32 fl. oz. [redacted] Plenvu [redacted] preparation contains 140 grams of PEG 3350, 48.11 grams of sodium ascorbate, 9 grams of sodium sulfate, 7.54 grams of ascorbic acid, 5.2 grams of sodium chloride and 2.2 grams of potassium chloride [redacted] the following excipients: aspartame [redacted], sucralose [redacted], encapsulated citric acid [redacted], and mango and fruit punch flavorings.

A mixing [redacted] for reconstitution is enclosed.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Plenvu (PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) is an osmotic laxative consisting of three pouches (one for Dose 1, one for Dose 2 Pouch A and one for Dose 2 Pouch B) containing white to yellow powder for reconstitution.	The proprietary name and established name are correctly expressed. **Satisfactory.**
Dosage form and route of administration	for oral solution containing white to yellow powder for reconstitution.	The dosage form, for oral solution, is expressed correctly, and route of administration, oral, is correctly presented . **Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)	Dose 1 contains 100 grams of PEG 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF; (b) (4) the following excipients: sucralose, NF (b) (4); encapsulated citric acid (b) (4) and mango flavoring. When Dose 1 is dissolved in water to a volume of 16 fl. oz., Plenvu Dose 1 (PEG 3350, sodium sulfate, sodium chloride, potassium chloride) is an oral solution having a mango (b) (4). Each Dose 2 Pouch A contains 40 grams of polyethylene glycol (PEG) 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 grams of potassium chloride, USP/NF; (b) (4) the following excipients: aspartame, NF (b) (4) and fruit punch flavoring. Each Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF and 7.54 grams of ascorbic acid, USP/NF. When Dose 2 Pouch A and Dose 2 Pouch B are dissolved together in water to a volume of 16 fl. oz., Plenvu Dose 2 (sodium ascorbate, PEG 3350, ascorbic acid, sodium chloride and potassium chloride) is an oral solution having a fruit punch (b) (4). The entire, reconstituted, 32 fl. oz. / (b) (4) Plenvu (b) (4) preparation contains 140 grams of PEG 3350, 48.11 grams of sodium ascorbate, 9 grams of sodium sulfate, 7.54 grams of ascorbic acid, 5.2 grams of sodium chloride and 2.2 grams of potassium chloride (b) (4) the following excipients: aspartame (b) (4), sucralose (b) (4), encapsulated citric acid (b) (4)	All strengths are expressed as active ingredients, not active moieties, and they are acceptable per salt policy for relatively simple inorganic compounds. **Satisfactory.**

	(b) (4), and mango and fruit punch flavorings.	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Dose 1 contains 100 grams of PEG 3350, NF; 9 grams of sodium sulfate, NF; 2 grams of sodium chloride, USP/NF; and 1 gram of potassium chloride, USP/NF; (b) (4) the following excipients: sucralose, NF (b) (4); encapsulated citric acid (b) (4) and mango flavoring. When Dose 1 is dissolved in water to a volume of 16 fl. oz., Plenvu Dose 1 (PEG 3350, sodium sulfate, sodium chloride, potassium chloride) is an oral solution having a mango (b) (4). Each Dose 2 Pouch A contains 40 grams of polyethylene glycol (PEG) 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 grams of potassium chloride, USP/NF; (b) (4) the following excipients: aspartame, NF (b) (4) and fruit punch flavoring. Each Dose 2 Pouch B contains 48.11 grams of sodium ascorbate, USP/NF and 7.54 grams of ascorbic acid, USP/NF. When Dose 2 Pouch A and Dose 2 Pouch B are dissolved together in water to a volume of 16 fl. oz., Plenvu Dose 2 (sodium ascorbate, PEG 3350, ascorbic acid, sodium chloride and potassium chloride) is an oral solution having a fruit punch (b) (4). The entire, reconstituted, 32 fl. oz. / (b) (4) Plenvu (b) (4) preparation contains 140 grams of PEG 3350, 48.11 grams of sodium ascorbate, 9 grams of sodium sulfate, 7.54 grams of ascorbic acid, 5.2 grams of sodium chloride and 2.2 grams of potassium chloride (b) (4) the following excipients: aspartame (b) (4), sucralose (b) (4), encapsulated citric acid (b) (4), and mango and fruit punch flavorings.	All inactive ingredients; sucralose NF and aspartame NF are listed by USP/NF names, except for encapsulated citric acid, mango flavoring, and fruit punch flavoring. Although they are not listed alphabetically, it is fine since FD&C Act requires it for only over-the-counter drugs. **Satisfactory.**
Statement of being sterile (if applicable)	NA	**N/A**
Pharmacological/ therapeutic class	osmotic laxative	**Satisfactory**
Chemical name, structural formula, molecular weight		Each active ingredient, PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid should be listed with their chemical name, chemical formulae, molecular weight, and structure. **Not Satisfactory.**
If radioactive, statement of	NA	NA

important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)	**NA**	NA

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

Plenvu is supplied as a white to yellow powder (b) (4) reconstitution.

(b) (4)

STORAGE

Store (b) (4) 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 (b) (4) may be stored in a refrigerator. (b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	Not included	"Plenvu is supplied as a white to yellow powder" needs to be revised to "Plenvu is supplied as powder to be reconstituted for oral solution: one pouch labeled Dose 1; two pouches labeled A and B for Dose 2 •• Pouch for 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; (b) (4) the following excipients: sucralose, NF (b) (4); encapsulated citric acid (b) (4); and mango flavoring (3). ••Pouch A for Dose 2 contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF; (b) (4) the following excipients: aspartame, NF (b) (4); and fruit punch flavoring (3). •• Pouch B for Dose 2 contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF (3). **Not Satisfactory.**
Available units (e.g., bottles of 100 tablets)	(b) (4)	**See above.** **Not Satisfactory.**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to yellow powder	**Satisfactory.**
Special handling (e.g., protect from light)	(b) (4)	The information provided is Adequate. **Satisfactory.**
Storage conditions	Store (b) (4) 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 (b) (4) may be stored in a refrigerator. (b) (4)	The information provided is Adequate. **Satisfactory.**

	hours after it is mixed in water.	
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Norgine B.V. Hogehilweg 7 1101CA Amsterdam ZO The Netherlands Product protected by U.S. Patent Numbers 8,999,313 and 9,326,969 B1. PLENVU, NORGINE and the sail logo are trademarks of the Norgine group of companies.	Included under Section 17 **Satisfactory.**

II. Labels

1. IMMEDIATE CONTAINER

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	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, 2.2 g)	Proprietary name, PLENVU, is presented. Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)" **Not Satisfactory.**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	Dose 1 contains: PEG 3350, 100 g; sodium sulfate, 9 g; sodium chloride, 2 g; potassium chloride, 1 g. This pouch contains 115.96 g of powder for oral solution. Dose 2 Pouch A contains: PEG 3350, 40 g; sodium chloride, 3.2 g; potassium chloride, 1.2 g. Also contains aspartame. This pouch contains 46.26 g of powder for oral solution. Dose 2 Pouch B contains: sodium ascorbate, 48.11 g; ascorbic acid, 7.54 g. This pouch contains 55.65 g of powder for oral solution.	**Satisfactory.**
Net contents	Dose 1 contains: PEG 3350, 100 g; sodium sulfate, 9 g; sodium chloride, 2 g; potassium chloride, 1 g. This pouch contains 115.96 g of powder for oral solution. Dose 2 Pouch A contains: PEG 3350, 40 g; sodium	**Satisfactory**

	chloride, 3.2 g; potassium chloride, 1.2 g. Also contains aspartame. This pouch contains 46.26 g of powder for oral solution. Dose 2 Pouch B contains: sodium ascorbate, 48.11 g; ascorbic acid, 7.54 g. This pouch contains 55.65 g of powder for oral solution.	
"Rx only" displayed prominently on the main panel	Displayed	**Satisfactory.**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	**Satisfactory.**
Lot number and expiration date (21 CFR 201.17)	Not Displayed	**Not Satisfactory.**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Displayed	**Satisfactory.**
Bar code (21CFR 201.25)	Displayed	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
And others, if space is available		

2. CARTON LABELS:

Secondary Carton:

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	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, 2.2 g)	Proprietary name is present. The font size of established name should be at least 50% of the tradename. The font color must be prominent as much as the tradename. **Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)"** **Not Satisfactory.**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	Not applicable	**N/A**
Net quantity of dosage form	Not displayed.	**Not Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed	**Satisfactory.**
Lot number and expiration date	Not Displayed	**Not Satisfactory.**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Displayed	**Satisfactory.**
Bar code (21CFR 201.25)	Displayed	**Satisfactory.**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	**Satisfactory.**
Manufacturer/distributor's name	Displayed	**Satisfactory.**
Quantitative ingredient information (injectables)	Displayed	**Satisfactory.**
Statement of being sterile (if applicable)	Displayed	**Satisfactory.**
"See package insert for dosage information"	Displayed	**Satisfactory.**
"Keep out of reach of children" (Required for OTC in CFR.	N/A	**N/A**

Optional for Rx drugs)		

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

- The title should be revised to;

  "Plenvu (PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)"

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- The Trade name should be included.

#11: Description

- The established name should be revised to;

  "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)"

- Each active ingredient; PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid should be listed with their chemical name, chemical formulae, molecular weight, and structure.

#16: How Supplied/Storage and Handling

- "Plenvu is supplied as a white to yellow powder" needs to be revised to

  "Plenvu is supplied as a white to yellow powder to be reconstituted for oral solution: One pouch labeled Dose 1; Two pouches labeled A and B for Dose 2
  •• The pouch for 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; (b) (4) the following excipients: sucralose, NF (b) (4) encapsulated citric acid (b) (4) and mango flavoring (3).
  •• Pouch A for Dose 2 contains 40 grams of PEG 3350, NF; 3.2 grams of sodium chloride, USP/NF; and 1.2 gram of potassium chloride, USP/NF; (b) (4) the following excipients: aspartame, NF (b) (4) and fruit punch flavoring (3).
  •• Pouch B for Dose 2 contains 48.11 grams of sodium ascorbate, USP/NF; and 7.54 grams of ascorbic acid, USP/NF (3).

B. Regarding of the Container/Carton Labels:

a) In immediate container label,

- Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)"
- Lot number and expiry date should be displayed.

b) Secondary carton

- Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)"
- The font size of established name should be at least 50% of the tradename.
- The font color must be prominent as much as the tradename.
- Lot number and expiry date should be displayed.

c) Tertiary carton should

- Revise established name to include parenthesis as follows "(PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution)"
- The font size of established name should be at least 50% of the tradename.
- The font color must be prominent as much as the tradename.
- Lot number and expiry date should be displayed.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

Overall, the labeling and labels need to be revised as delineated in the List of Deficiencies.

Recommendation:

From the ONDP perspective, this application is ***not*** deemed ready for approval per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Sarah Ibrahim, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Ibrahim's assessment of the labels and labeling and her recommendation that this application is not ready as it is until the deficiencies are resolved satisfactorily.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Sarah Ibrahim

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Moo Jhong Rhee

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Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 209381 Plenvu for oral solution

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Assays of the the drug substances (polyethylene glycol 3350, sodium ascorbate and ascorbic acid) were determined by the in-house validated HPLC method. During manufacturing process development critical steps were identified and in process controls (IPC) e.g. (b) (4) to constistantly produce quality DP. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters • Container/closure system	L	The related substances/ impurities are fully characterized and controlled by DS specification. The impurities are also controlled by DP specification at release and on stability. The impurities are assessed by the in-house validated HPLC and/or GC methods.	Low to None	None

Hitesh Shroff

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