CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 203595
Product Name: SUCLEAR

PMR/PMC Description: An adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in adult patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking Suclear prior to colonoscopy. Serial laboratory and clinical assessments should be done at regular pre-specified intervals for at least 30 days post-treatment.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	06/01/2014
Study/Trial Completion:	06/01/2016
Final Report Submission:	12/01/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The short-term safety profile of SUCLEAR appears similar to other approved bowel cleansing products.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In clinical trials, data to assess renal effects and serum laboratory abnormalities were limited to the immediate post-treatment period without longer term follow-up. There were some patients with normal baseline laboratory parameters that shifted to abnormal after treatment with SUCLEAR without subsequent follow up to assess reversibility of the findings (e.g., CK, ALT, eGFR). The clinical significance of these changes remains unknown but could potentially reflect a safety risk or prompt label revisions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in adult patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking Suclear prior to colonoscopy. Serial laboratory and clinical assessments should be done at regular pre-specified intervals for at least 30 days post-treatment.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 203595
Product Name: SUCLEAR

PMR/PMC Description: Assess the systemic exposure and pharmacokinetics of PEG3350, [redacted] (b) (4) following oral administration of SUCLEAR to adult subjects.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	06/01/2014
Study/Trial Completion:	06/01/2016
Final Report Submission:	12/01/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The short-term safety profile of SUCLEAR appears similar to other approved bowel cleansing products that contain PEG3350.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

[redacted] and [redacted] are known toxins and are present as impurities within PEG3350. Furthermore, [redacted] and [redacted] are [redacted] However, the absorption and pharmacokinetics of PEG3350 including [redacted], and [redacted] are not well described for bowel cleansing agents that contain these compounds. Exposures to these compounds were not evaluated in the clinical studies of SUCLEAR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assess the systemic exposure and pharmacokinetics of PEG3350, (b) (4) ollowing oral administration of SUCLEAR to adult subjects. These assessments may be conducted as a sub-study of PMR #1

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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

/s/

ROBERT FIORENTINO
01/18/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**SUCLEAR (sodium sulfate, potassium sulfate and magnesium sulfate oral solution; and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)**
Applicant	Braintree Laboratories, Inc.
Application/Supplement Number	NDA 203595
Type of Application	Original Submission (NME)
Indication(s)	For cleansing of the colon in preparation for colonoscopy in adults
Established Pharmacologic Class[1]	Combination of Osmotic Laxatives
Office/Division	ODE III/DGIEP
Division Project Manager	Matthew Scherer
Date FDA Received Application	December 19, 2011
Goal Date	January 19, 2013
Date PI Received by SEALD	January 11, 2013
SEALD Review Date	January 12, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Provided DGIEP with suggestions for reducing HL to 1/2 page; if HL not reduced, approval letter must reflect that waiver will be granted.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

NO 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment: *Horizontal line is missing. Insert.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *In both places, name of drug product is in sentence case (i.e., Suclear) and not upper case (i.e., SUCLEAR). Change to upper case (i.e., SUCLEAR).*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Initial U.S. approval is not placed immediately beneath the product title and appears as "01/2013" (i.e., month/year); must appear as 4-digit year (i.e., 2013). Delete the month.*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.
Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: *For Dosage and Administration section, subsection headings 2.1, 2.2, and 2.3 are missing from the TOC. Insert. In addition, delete subsection 17.1 Patient Counseling from the TOC; it does not appear in the FPI and is not necessary.*

N/A

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *The Medication Guide does not appear at the end of the PI; must appear at the end of the PI upon approval.*

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *Cross reference in subsection 8.6 should not be bolded and only appear in italics.*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

JEANNE M DELASKO
01/12/2013

LAURIE B BURKE
01/14/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	December 31, 2012
Reviewer(s):	Patty Greene, Pharm.D., Drug Use Data Analyst Division of Epidemiology II (DEPI II)
Team Leader	Grace Chai, Pharm.D. Division of Epidemiology II (DEPI II)
Deputy Director	Laura Governale, Pharm.D., MBA Division of Epidemiology II (DEPI II)
Subject:	Polyethylene Glycol 3350 Pediatric Drug Utilization
Drug Name(s):	Polyethylene Glycol 3350 (MiraLAX, Colyte®, GoLytely®, HalfLytely®, Moviprep®, and NuLytely®)
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
OSE RCM #:	2012-1517

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY

This review examines pediatric drug utilization of polyethylene glycol 3350 products from year 2002 through year-to-date October 2012.

Sales Distribution Data:

- Sales distribution data for polyethylene glycol 3350 products showed that approximately 24.1 million bottles were distributed to all US channels of distribution in year 2011, a decrease of 25% from approximately 32.2 million bottles in year 2007.
    - Sales of prescription polyethylene glycol 3350 products decreased by 46% while over-the-counter products increased by 124% since year 2007.

Outpatient Retail Prescription Data:

- For the entire review period, 102 million prescriptions were dispensed for polyethylene glycol 3350 products.
    - Among the pediatric population (age 0-16 years), dispensed prescriptions of polyethylene glycol 3350 products accounted for 13% (12.9 million prescriptions) of total dispensed prescriptions for the entire review period.
- Approximately 10.4 million prescriptions were dispensed for polyethylene glycol 3350 products in year 2011, double the number of prescriptions dispensed (5.2 million prescriptions) in year 2002.
- Although NuLytely and generic equivalents are the only approved prescription polyethylene 3350 products in the pediatric population, MiraLAX and generic equivalents accounted for the largest proportion of pediatric prescriptions (99% or 12.8 million prescriptions) for the review period.

Office-Based Physician Survey Data:

- According to office-based physician survey, MiraLAX was the most common product associated with use for the diagnosis of constipation or abdominal pain in the pediatric population in year 2011.

1 INTRODUCTION

Using currently available proprietary drug utilization databases, this review describes the sales of prescription and over-the-counter (OTC) polyethylene glycol 3350 products nationwide, as well as outpatient prescription utilization of polyethylene glycol 3350 products in the pediatric population from years 2002 through year-to-date October 2012.

1.1 BACKGROUND

On June 6, 2012, Empire State Consumer Project submitted a Citizen's Petition concerning the risk of adverse events and death associated with using polyethylene glycol 3350 products in the pediatric population. The Petition requests that FDA: 1) immediately recall PEG 3350 products to add a boxed warning advising against the use of the drug in children and warning of potential adverse events associated with the use of the drug; 2) conduct an investigation of the relationship between [redacted] (b) (4) toxicity symptoms, [redacted] (b) (4) toxicity symptoms, and the polyethylene glycol adverse

events reported by parents of children taking polyethylene glycol; 3) review and disclose the results of completed clinical trials on PEG 3350 products that have not been published; 4) investigate the long term effects of short term use of polyethylene glycol 3350 on human health; 5) investigate the long term effects of long term use of PEG 3350 on human health; 6) investigate the long term effects of short term and long term use of PEG 3350 in pediatric patients; 7) investigate the effects of PEG 3350 use in treating chronic constipation.[1]

In addition, the Division of Gastroenterology and Inborn Errors Products (DGIEP) has requested a review of drug utilization data for Colyte, GoLytely, HalfLytely, Moviprep, NuLytely, and their generic equivalents to determine an appropriate comparator for studies of (b) (4) in the pediatric population. (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350, (b) (4) is an osmotic laxative with a new drug application for cleansing of the colon in preparation for colonoscopy in adults.[2] The sponsor of (b) (4) Braintree Laboratories, Inc., submitted a pediatric plan for a clinical study in pediatric subjects in accordance with the requirements of the Pediatric Research Equity Act (PREA). The pediatric plan was reviewed by the Pediatric Review Committee (PeRC) on August 1, 2012. NuLytely is the only PEG 3350 product approved for use in the pediatric population. NuLytely is indicated for bowel cleansing prior to colonoscopy in patients ages 6 months and older.[3] All other PEG 3350 products are not approved for pediatric use.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for polyethylene glycol 3350 products. Sales data for the 12-month period ending in October 2012 indicated that approximately 73% of packages (Eaches) were distributed to outpatient retail pharmacies; 23% were to non-retail settings; and 4% were to mail-order/specialty pharmacies.[4] As a result, outpatient retail utilization patterns were examined. Neither mail-order/specialty nor non-retail settings data were included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full data description).

IMS Health, IMS National Sales Perspectives™ was used to determine national estimates of the number of bottles and packages (eaches) sold for polyethylene glycol 3350

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[1] Heavner, Carolina Request for Consult on Citizen Petition (FDA-2012-P-0566) July 2012

[2] (b) (4) Draft Prescribing Information October 2011

[3] Nulytely label. http://www.nulytely.com/

[4] IMS Health, IMS National Sales Perspectives™. Nov 2011-Oct 2012 Extracted December 2012. File: NSPC 2012-1517 PEG Product sales 12-11-12.xlsx

products by prescription status (over-the-counter or prescription) from manufacturers into retail and non-retail markets from year 2007 through 2011 and year-to-date October 2012.

IMS, Vector One®: National (VONA) was used to determine national estimates of the number of outpatient dispensed prescriptions for polyethylene glycol 3350 products, stratified by patient age (0-<1, 1-2, 3-16, and 17+ years), from year 2002 through 2011 and year-to-date October 2012.

Encuity Research, LLC., TreatmentAnswers™ was used to examine the use of laxative products (USC Class:56520 [Hyperosmolar Laxatives], 56700 [Pre-Xray Evacuants], 56900 [Other Laxatives]) by patient age and diagnoses as reported by U.S. office-based physician survey for year 2011.

2.3 PRODUCTS INCLUDED

All prescription polyethylene glycol 3350/potassium chloride/sodium bicarbonate/sodium chloride products including MiraLAX, Colyte, GoLytely, HalfLytely, Moviprep, NuLytely, and generic equivalents were included in this review.

Table 1: Formulations of polyethylene glycol 3350 products [5]

Trade Name	Application Number	Original Approval Date	Indication	Pediatric Approval
NuLytely	NDA 19-797 and various ANDAs	4/22/1991	Indicated for bowel cleansing prior to colonoscopy.	**Yes 6 months and older**
MiraLAX	NDA 20-698 NDA 22-015 (OTC) and various ANDAs	2/18/1999 10/6/2006	For the treatment of occasional constipation	No
Colyte	NDA 18-983 and various ANDAs	10/26/1984	Bowel cleansing prior to colonoscopy or barium enema X-ray examination	No
GoLytely	NDA 19-011 and various ANDAs	7/13/1984	Bowel cleansing prior to colonoscopy or barium enema X-ray examination	No
HalfLytely	NDA 21-551	5/10/2004	Cleansing of the colon as a preparation for colonoscopy in adults	No
Moviprep	NDA 21-881	8/2/2006	Indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years or older.	No

[5] PEG 3350 product labels. http://dailymed nlm nih.gov/dailymed/about.cfm

3 RESULTS

3.1 NATIONAL SALES OF POLYETHYLENE GLYCOL 3350 PRODUCTS

Table 1 in Appendix 1 provides the nationally estimated number of bottles/packages of polyethylene glycol 3350 products sold from manufacturers to U.S. retail and non-retail channels of distribution for years 2007 through 2011 and year-to-date October 2012. Approximately 24.1 million bottles were distributed for polyethylene glycol 3350 products in year 2011, a decrease of 25% from approximately 32.2 million bottles in year 2007. Prescription polyethylene glycol 3350 products decreased by 46% while OTC polyethylene glycol 3350 products increased by 124% since year 2007. In year 2011, *prescription* polyethylene glycol 3350 products accounted for 63% (15.3 million bottles) of the total market and *OTC* polyethylene glycol 3350 accounted for 37% (8.8 million bottles) of the total market. Generic polyethylene glycol was the most commonly dispensed prescription product in terms of sales at 65% (9.9 million bottles) followed by Moviprep at 10% (approximately 1.6 million bottles) in year 2011. All other prescription polyethylene glycol 3350 products each accounted for less than 7% of the selected market.

MiraLAX (OTC) was the most commonly distributed OTC polyethylene glycol 3350 product at 63% (5.6 million bottles) followed by generic polyethylene glycol 3350 at 35% (approximately 3.1 million bottles) in year 2011. All other OTC polyethylene glycol 3350 products each accounted for less than 1% of the selected market. Sales of MiraLAX (OTC) peaked in year 2009 accounting for 98% of OTC polyethylene glycol 3350 sales. However, OTC market share for MiraLAX (OTC) decreased by 28% since 2009 mainly due to an increase in sales of generic polyethylene glycol 3350.

3.2 DISPENSED PRESCRIPTIONS BY PATIENT AGE IN OUTPATIENT RETAIL PHARMACIES

Table 2 and Figure 1 in Appendix 1 show the nationally estimated number of dispensed prescriptions for polyethylene glycol 3350 products and generic equivalents by patient age (0-16, 17+ years) in U.S. outpatient retail pharmacies for year 2002 through 2011 and year-to-date October 2012. For the entire review period, 102 million prescriptions were dispensed for polyethylene glycol 3350 products. The number of prescriptions dispensed doubled from approximately 5.2 million prescriptions in year 2002 to 10.4 million prescriptions in year 2011. Prescription utilization increased since year 2002 for all products except Colyte and Nulytely. Dispensed prescriptions of Colyte and Nulytely decreased by 39% and 19%, respectively. In 2011, MiraLAX and generic equivalents accounted for the largest proportion of dispensed prescription at 51% (5.3 million prescriptions), followed by Moviprep at 13% (approximately 1.4 million prescriptions), HalfLytely at 11% (approximately 1.2 million prescriptions), Nulytely at 10% (1 million prescriptions), and followed by Colyte and Golytely at 8% (approximately 800,000 prescriptions each) respectively.

Among the pediatric population (age 0-16 years), total dispensed prescriptions of polyethylene glycol 3350 accounted for 13% (approximately 12.9 million prescriptions) compared to adults (17 years and older) at 87% (89.3 million prescriptions) for the entire

review period. MiraLAX and generic equivalents accounted for the largest proportion of dispensed prescriptions at 99% (1.2 million prescriptions) of prescriptions dispensed to the pediatric population in year 2011.

Table 3 and Figure 3 in Appendix 1 show the nationally estimated number of dispensed prescriptions for polyethylene glycol 3350 and generic equivalents dispensed to the *pediatric population*, by patient age (0-<1, 1-2, 3-16 years), in U.S. outpatient retail pharmacies for year 2002 through 2011 and year-to-date October 2012. MiraLAX prescriptions accounted for the majority of polyethylene glycol 3350 products dispensed to the pediatric population throughout the examined time, accounting for 98% to >99% of the pediatric prescriptions, annually. Prescriptions dispensed to the pediatric population for MiraLAX nearly tripled from 646,000 prescriptions dispensed in year 2002 to a peak of 1.8 million prescriptions dispensed in year 2006. MiraLAX switched from prescription to over-the-counter status in year 2006. From year 2007 to 2011, the number of pediatric prescriptions of MiraLAX decreased 21% from approximately 1.5 million prescriptions in year 2007 to 1.2 million prescriptions in year 2011. The majority of prescriptions were dispensed to pediatric patients aged 3-16 years throughout the examined time. Less than 2% of prescriptions for each respective product group were dispensed to patients <1 year of age for the review period.

Figure 4 in Appendix 1 shows the nationally estimated number of prescriptions for bowel prep polyethylene glycol 3350 products (Colyte, GoLytely, HalfLytely, Moviprep, NuLytely, and generic equivalents), *excluding MiraLAX and generics*, dispensed to the pediatric population (0-16 years) from U.S. outpatient retail pharmacies for year 2002 through 2011. Prescription utilization for bowel prep products increased by 4% overall since year 2002 and ranged from 12,000 to 18,000 prescriptions annually. Prescriptions dispensed for Nulytely and generics, the only polyethylene glycol 3350 product approved for use in the pediatric population, decreased 61.5% from 5,042 prescriptions dispensed in year 2002 to 1,941 prescriptions dispensed in year 2011.

3.3 LAXATIVE PRODUCT USE BY PATIENT AGE AND DIAGNOSES

We also examined drug use mentions[6] for laxative products (USC Classes: 56520, 56700, 56900) by patient age for the top diagnoses associated with use as reported by office-based physician practices in year 2011. "Constipation" (ICD-9 564.0) was the most frequently reported diagnosis accounting for 100%, 96%, and 77% of use mentions in pediatric patients aged <1 year, 1-2 years, and 3-16 years, respectively. Among adults aged 17 years and older, "Constipation" (ICD-9 564.0) accounted for approximately 20% of drug use mentions for these laxative products. Diagnoses for "Abdominal Pain" (ICD-9 789.0) were also reported among the top diagnoses in pediatric patients aged 1-2 and 3-16 years, accounting for 4% and 14% of use mentions, respectively. The top product associated with use for the selected GI diagnoses in the pediatric population was

[6] The term "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

MiraLAX, accounting for 84% to 100% of drug use mentions for each diagnosis for the respective age groups within the pediatric population (***Table 4 in Appendix 1***).

4 DISCUSSION

Our findings show that approximately 13% of prescriptions (approximately 12.9 million out of a total of 102 million prescriptions) were dispensed to the pediatric population for polyethylene glycol 3350 products during the entire study period, 2002 through 2011. Although NuLytely and generic equivalents are the only approved prescription polyethylene 3350 products in the pediatric population, MiraLAX and generic equivalents were the most commonly dispensed products to the pediatric population accounting for 12.8 million (99%) of pediatric prescriptions compared to less than 1% for all other polyethylene glycol products for the review period. Off-label pediatric use of polyethylene glycol 3350 was also identified for Golytely, HalfLytely, Moviprep, and Colyte.

Although the review provides a descriptive analysis of polyethylene glycol 3350 prescription products in the pediatric population, the data may underrepresent the actual volume of pediatric use in the outpatient retail setting for several reasons. First, our prescription analysis was limited to prescription polyethylene glycol 3350 products available in the IMS VONA database. Secondly, according to IMS sales data, nearly a third of polyethylene glycol 3350 is available for purchase without a prescription in the retail pharmacy setting. However, it is not uncommon for pharmacists to dispense OTC polyethylene glycol 3350 as a prescription for patients using commercial insurance, flexible spending or health savings accounts. We examined Shopper Insights Advantage™ (SIA) to estimate the number of households with pediatric patients (<17 years) purchasing MiraLAX in the U.S. for year 2009 through 2011. Though SIA provides product purchasing data at the household level, national estimates of pediatric use were not available.

According to office-based physician survey data in year 2011, MiraLAX appears to be the most prescribed product to the pediatric population for the most common GI diagnoses reported (e.g. constipation, abdominal pain, etc.) in the outpatient office based setting. Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that polyethylene glycol 3350 and their generic equivalents are distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail

channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The estimates provided are national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

5 CONCLUSIONS

The pediatric population accounted for 13% (approximately 12.9 million out of a total of 102 million prescriptions) of polyethylene glycol 3350 dispensed prescriptions from U.S. outpatient retail pharmacies during the examined time. Although NuLytely and generic equivalents are the only approved prescription polyethylene 3350 products in the pediatric population, MiraLAX and generic equivalents accounted for the largest proportion of pediatric prescriptions (99% or 12.8 million prescriptions) for the review period. According to office-based physician survey data in year 2011, MiraLAX was the top drug product mentioned for the most commonly reported GI diagnosis of "Constipation" in the pediatric population. However, these analysis likely represent an underestimate of the true extent of pediatric use of MiraLAX as the product is primarily available over-the-counter according to sales distribution data. Off-label pediatric use of HalfLytely, Moviprep, Colyte, GoLytely, and their generic equivalents was also found during the examined time.

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Table 1: Nationally estimated number of bottles and packages of polyethylene glycol 3350 products sold from manufacturers to U.S. retail and non-retail channels of distribution, years 2007 - 2011 and year-to-date Oct 2012

	2007		2008		2009		2010		2011		YTD Oct 2012	
	Eaches	Share	Eaches	Share	Eaches	Share	Eaches	Share	Eaches	Share	Eaches	Share
	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	32,169,005	100.0%	20,215,478	100.0%	23,435,969	100.0%	22,876,728	100.0%	24,101,989	100.0%	21,298,650	100.0%
Rx	28,232,608	87.8%	14,261,773	70.6%	15,531,963	66.3%	15,263,639	66.7%	15,276,096	63.4%	13,048,214	61.3%
POLYETHYLENE GLY(RX)	3,630,406	12.9%	6,902,108	48.4%	8,062,064	51.9%	9,081,622	59.5%	9,936,636	65.1%	7,633,598	58.5%
MOVIPREP	563,267	2.0%	726,854	5.1%	1,277,161	8.2%	1,551,125	10.2%	1,558,601	10.2%	1,184,789	9.1%
PEG 3350/ELECTROLYTES	818,925	2.9%	795,956	5.6%	966,594	6.2%	966,396	6.3%	951,296	6.2%	990,042	7.6%
GLYCOLAX (RX)	18,548,424	65.7%	1,040,725	7.3%	19,787	0.1%	18,829	0.1%	50,312	0.3%	951,748	7.3%
GOLYTELY	1,260,331	4.5%	1,379,838	9.7%	1,471,128	9.5%	1,140,603	7.5%	1,034,422	6.8%	876,952	6.7%
HALFLYTELY	1,356,056	4.8%	1,414,108	9.9%	1,747,213	11.3%	1,078,903	7.1%	465,164	3.1%	334,095	2.6%
GAVILYTE-N					108,255	0.7%	324,798	2.1%	310,000	2.0%	298,150	2.3%
TRILYTE	1,082,389	3.8%	1,048,555	7.4%	994,844	6.4%	282,397	1.9%	241,893	1.6%	272,822	2.1%
GAVILYTE-G					182,231	1.2%	358,221	2.4%	318,518	2.1%	167,598	1.3%
GAVILYTE-C					39,680	0.3%	131,535	0.9%	163,633	1.1%	156,258	1.2%
NULYTELY	655,743	2.3%	732,369	5.1%	484,831	3.1%	218,487	1.4%	171,371	1.1%	123,801	1.0%
COLYTE W/ FLAV PACK	250,726	0.9%	202,834	1.4%	177,396	1.1%	110,263	0.7%	73,679	0.5%	42,977	0.3%
MIRALAX (RX)	63,337	0.2%	18,415	0.1%	66	0.0%	30	0.0%			14,838	0.1%
PEG 3350-GRX					711	0.0%	430	0.0%	571	0.0%	546	0.0%
COLYTE	230	0.0%	8	0.0%	2	0.0%						
COLYTE-FLAVORED	2,774	0.0%	3	0.0%								
OTC	3,936,397	12.2%	5,953,705	29.5%	7,904,006	33.7%	7,613,089	33.3%	8,825,893	36.6%	8,250,436	38.7%
MIRALAX (OTC)	3,936,397	100.0%	5,953,705	100.0%	7,713,397	97.6%	6,029,853	79.2%	5,553,458	62.9%	5,519,702	66.9%
POLYETHYLENE GLY(OTC)					190,285	2.4%	1,561,860	20.5%	3,091,703	35.0%	2,435,593	29.5%
GAVILAX					324	0.0%	13,870	0.2%	117,579	1.3%	220,907	2.7%
HEALTHYLAX							7,295	0.1%	63,139	0.7%	74,204	0.9%
GLYCOLAX (OTC)							211	0.0%	14	0.0%	30	0.0%

Source: IMS Health, IMS National Sales Perspective™. Years 2007-YTD Oct 2012. Extracted December 2012. Files: NSPC 2012-1517 PEG by Rx Status 12-14-12.xls
Eaches (EA) - This measure represents the number of single items (such as bottles) contained in a unit or shipping package and purchased by providers

Figure 1: Nationally estimated number of dispensed prescriptions for MiraLAX and generic equivalents by patient age (0-16, 17+ years) in U.S. outpatient retail pharmacies, years 2002-2011

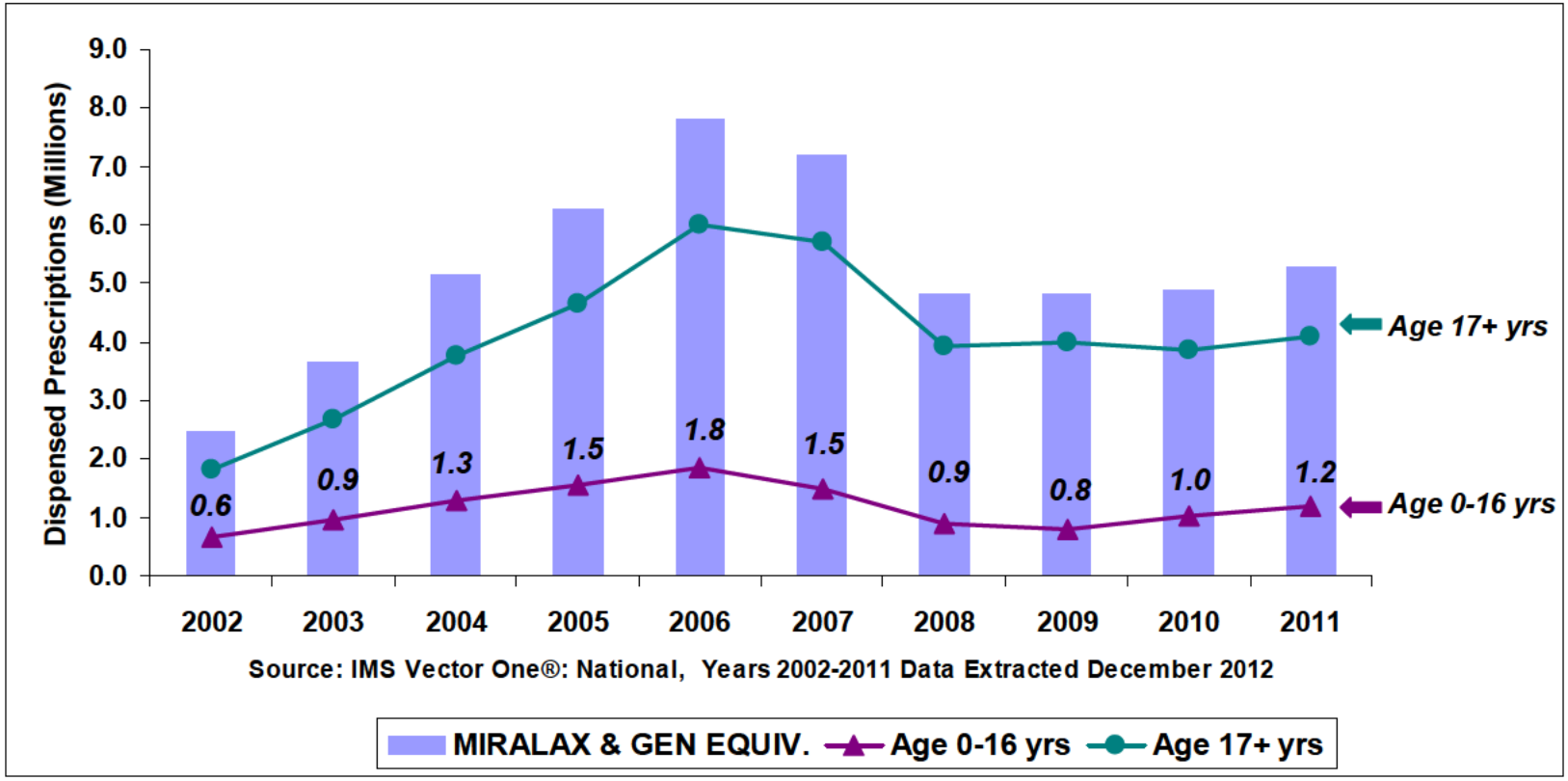

Table 2. Nationally estimated number of dispensed prescriptions for polyethylene glycol 3350 products and generic equivalents by patient age (0-16, 17+ years) in U.S. outpatient retail pharmacies, years 2002 - 2011 and year-to-date Oct 2012

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		YTD OCT 2012		Grand Total	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	5,214,857	*100.0%*	6,343,839	*100.0%*	7,741,178	*100.0%*	9,249,644	*100.0%*	11,571,569	*100.0%*	11,621,687	*100.0%*	9,699,800	*100.0%*	10,954,239	*100.0%*	10,637,155	*100.0%*	10,406,445	*100.0%*	9,037,363	*100.0%*	102,477,778	*100.0%*
Age 0-16 yrs	660,858	*12.7%*	962,722	*15.2%*	1,295,905	*16.7%*	1,551,256	*16.8%*	1,849,212	*16.0%*	1,505,965	*13.0%*	916,407	*9.4%*	823,121	*7.5%*	1,039,591	*9.8%*	1,191,108	*11.4%*	1,143,111	*12.6%*	12,945,823	*12.6%*
Age 17+ yrs	4,524,802	*86.8%*	5,333,378	*84.1%*	6,354,447	*82.1%*	7,612,546	*82.3%*	9,721,871	*84.0%*	10,115,357	*87.0%*	8,783,288	*90.6%*	10,128,186	*92.5%*	9,595,191	*90.2%*	9,214,511	*88.5%*	7,893,568	*87.3%*	89,277,146	*87.1%*
Unknown Age	29,195	*0.6%*	47,739	*0.8%*	84,256	*1.1%*	85,842	*0.9%*	486	*0.0%*	364	*0.0%*	103	*0.0%*	2,932	*0.0%*	2,373	*0.0%*	827	*0.0%*	685	*0.0%*	254,801	*0.2%*
MIRALAX & GEN EQUIV.	2,487,700	*47.7%*	3,644,315	*57.4%*	5,131,236	*66.3%*	6,269,128	*67.8%*	7,821,029	*67.6%*	7,187,824	*61.8%*	4,812,318	*49.6%*	4,812,841	*43.9%*	4,883,465	*45.9%*	5,261,464	*50.6%*	4,790,968	*53.0%*	57,102,288	*55.7%*
Age 0-16 yrs	645,634	*26.0%*	948,720	*26.0%*	1,290,383	*25.1%*	1,539,492	*24.6%*	1,835,797	*23.5%*	1,491,136	*20.7%*	900,922	*18.7%*	805,203	*16.7%*	1,022,200	*20.9%*	1,175,324	*22.3%*	1,129,074	*23.6%*	12,783,884	*22.4%*
Age 17+ yrs	1,823,341	*73.3%*	2,663,842	*73.1%*	3,770,935	*73.5%*	4,657,304	*74.3%*	5,984,867	*76.5%*	5,696,415	*79.3%*	3,911,330	*81.3%*	4,004,925	*83.2%*	3,859,503	*79.0%*	4,085,434	*77.6%*	3,661,245	*76.4%*	44,119,140	*77.3%*
Unknown Age	18,725	*0.8%*	31,753	*0.9%*	69,918	*1.4%*	72,332	*1.2%*	366	*0.0%*	273	*0.0%*	65	*0.0%*	2,713	*0.1%*	1,762	*0.0%*	707	*0.0%*	649	*0.0%*	199,263	*0.3%*
NULYTELY AND GEN EQUIV.	1,252,770	*24.0%*	1,222,405	*19.3%*	1,253,379	*16.2%*	1,183,030	*12.8%*	1,425,491	*12.3%*	1,493,703	*12.9%*	1,621,935	*16.7%*	1,821,575	*16.6%*	1,176,187	*11.1%*	1,012,895	*9.7%*	884,308	*9.8%*	14,347,678	*14.0%*
Age 0-16 yrs	5,042	*0.4%*	4,756	*0.4%*	4,011	*0.3%*	3,177	*0.3%*	3,127	*0.2%*	3,219	*0.2%*	3,023	*0.2%*	3,201	*0.2%*	1,963	*0.2%*	1,941	*0.2%*	1,713	*0.2%*	35,173	*0.2%*
Age 17+ yrs	1,243,402	*99.3%*	1,207,578	*98.8%*	1,242,742	*99.2%*	1,174,703	*99.3%*	1,422,316	*99.8%*	1,490,462	*99.8%*	1,618,905	*99.8%*	1,818,332	*99.8%*	1,174,105	*99.8%*	1,010,904	*99.8%*	882,582	*99.8%*	14,286,031	*99.6%*
Unknown Age	4,326	*0.3%*	10,071	*0.8%*	6,626	*0.5%*	5,150	*0.4%*	47	*0.0%*	22	*0.0%*	7	*0.0%*	41	*0.0%*	119	*0.0%*	50	*0.0%*	14	*0.0%*	26,474	*0.2%*
HALFLYTELY AND GEN EQUIV.					83,597	*1.1%*	836,218	*9.0%*	1,229,293	*10.6%*	1,299,828	*11.2%*	1,409,339	*14.5%*	1,723,177	*15.7%*	1,792,402	*16.9%*	1,156,549	*11.1%*	836,081	*9.3%*	10,366,484	*10.1%*
Age 0-16 yrs					238	*0.3%*	2,002	*0.2%*	2,882	*0.2%*	3,267	*0.3%*	3,686	*0.3%*	3,950	*0.2%*	4,085	*0.2%*	2,688	*0.2%*	2,203	*0.3%*	25,000	*0.2%*
Age 17+ yrs					83,079	*99.4%*	831,956	*99.5%*	1,226,378	*99.8%*	1,296,526	*99.7%*	1,405,643	*99.7%*	1,719,177	*99.8%*	1,788,180	*99.8%*	1,153,836	*99.8%*	833,878	*99.7%*	10,338,654	*99.7%*
Unknown Age					280	*0.3%*	2,260	*0.3%*	33	*0.0%*	36	*0.0%*	10	*0.0%*	50	*0.0%*	137	*0.0%*	25	*0.0%*	--	--	2,830	*0.0%*
COLYTE AND GEN EQUIV.	1,324,611	*25.4%*	1,365,131	*21.5%*	1,176,509	*15.2%*	857,767	*9.3%*	947,874	*8.2%*	954,480	*8.2%*	894,328	*9.2%*	1,056,316	*9.6%*	789,650	*7.4%*	807,853	*7.8%*	643,916	*7.1%*	10,818,434	*10.6%*
Age 0-16 yrs	7,446	*0.6%*	7,586	*0.6%*	6,568	*0.6%*	5,185	*0.6%*	5,610	*0.6%*	5,501	*0.6%*	4,764	*0.5%*	5,746	*0.5%*	3,421	*0.4%*	2,714	*0.3%*	1,996	*0.3%*	56,538	*0.5%*
Age 17+ yrs	1,312,147	*99.1%*	1,352,649	*99.1%*	1,163,555	*98.9%*	847,349	*98.8%*	942,226	*99.4%*	948,950	*99.4%*	889,551	*99.5%*	1,050,492	*99.4%*	786,126	*99.6%*	805,130	*99.7%*	641,905	*99.7%*	10,740,080	*99.3%*
Unknown Age	5,018	*0.4%*	4,896	*0.4%*	6,386	*0.5%*	5,233	*0.6%*	38	*0.0%*	28	*0.0%*	13	*0.0%*	77	*0.0%*	103	*0.0%*	9	*0.0%*	15	*0.0%*	21,815	*0.2%*
MOVIPREP									26,606	*0.2%*	504,678	*4.3%*	683,962	*7.1%*	1,120,637	*10.2%*	1,344,986	*12.6%*	1,378,151	*13.2%*	1,095,871	*12.1%*	6,154,891	*6.0%*
Age 0-16 yrs									59	*0.2%*	731	*0.1%*	902	*0.1%*	1,271	*0.1%*	1,337	*0.1%*	1,138	*0.1%*	873	*0.1%*	6,311	*0.1%*
Age 17+ yrs									26,548	*99.8%*	503,941	*99.9%*	683,052	*99.9%*	1,119,348	*99.9%*	1,343,483	*99.9%*	1,376,985	*99.9%*	1,094,998	*99.9%*	6,148,355	*99.9%*
Unknown Age											5	*0.0%*	7	*0.0%*	18	*0.0%*	167	*0.0%*	28	*0.0%*	--	--	225	*0.0%*
GOLYTELY AND GEN EQUIV.	149,774	*2.9%*	111,988	*1.8%*	96,455	*1.2%*	103,501	*1.1%*	121,275	*1.0%*	181,175	*1.6%*	277,918	*2.9%*	419,695	*3.8%*	650,464	*6.1%*	789,533	*7.6%*	786,218	*8.7%*	3,687,997	*3.6%*
Age 0-16 yrs	2,736	*1.8%*	1,660	*1.5%*	1,273	*1.3%*	1,400	*1.4%*	1,737	*1.4%*	2,111	*1.2%*	3,110	*1.1%*	3,750	*0.9%*	6,585	*1.0%*	7,303	*0.9%*	7,252	*0.9%*	38,917	*1.1%*
Age 17+ yrs	145,912	*97.4%*	109,309	*97.6%*	94,136	*97.6%*	101,234	*97.8%*	119,536	*98.6%*	179,063	*98.8%*	274,807	*98.9%*	415,912	*99.1%*	643,794	*99.0%*	782,222	*99.1%*	778,960	*99.1%*	3,644,886	*98.8%*
Unknown Age	1,126	*0.8%*	1,019	*0.9%*	1,046	*1.1%*	867	*0.8%*	2	*0.0%*			1	*0.0%*	33	*0.0%*	85	*0.0%*	8	*0.0%*	7	*0.0%*	4,194	*0.1%*

Source: IMS Vector One®: National, Years 2002-YTD Oct 2012 Data Extracted Dec 2012. File: VONA 2012-1517 FDA_PEG-3350_PED_Grouped 12-5-12.xls

Table 3: Nationally estimated number of prescriptions for polyethylene glycol 3350 and generic equivalents dispensed to the *pediatric population* by patient age (<1, 1-2, 3-16 years) in U.S. outpatient retail pharmacies, years 2002 - 2011 and year-to-date Oct 2012

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		YTD Oct 2012		Grand Total	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	660,858	*100.0%*	962,722	*100.0%*	1,302,473	*100.0%*	1,551,256	*100.0%*	1,849,212	*100.0%*	1,505,966	*100.0%*	916,407	*100.0%*	823,121	*100.0%*	1,039,592	*100.0%*	1,191,108	*100.0%*	1,143,110	*100.0%*	12,945,824	*100.0%*
MIRALAX & GEN	**645,634**	***97.7%***	**948,720**	***98.5%***	**1,290,383**	***99.1%***	**1,539,492**	***99.2%***	**1,835,797**	***99.3%***	**1,491,136**	***99.0%***	**900,922**	***98.3%***	**805,203**	***97.8%***	**1,022,200**	***98.3%***	**1,175,324**	***98.7%***	**1,129,074**	***98.8%***	**12,783,884**	***98.7%***
Age <1	3,500	*0.5%*	5,674	*0.6%*	9,617	*0.7%*	11,366	*0.7%*	34,862	*1.9%*	22,866	*1.5%*	10,725	*1.2%*	13,211	*1.6%*	23,151	*2.3%*	28,594	*2.4%*	27,802	*2.5%*	191,369	*1.5%*
Age 1 to 2 yrs	83,519	*12.9%*	127,136	*13.4%*	181,222	*14.0%*	210,738	*13.7%*	326,420	*17.8%*	251,375	*16.9%*	138,659	*15.4%*	118,774	*14.8%*	154,744	*15.1%*	173,688	*14.8%*	162,288	*14.4%*	1,928,562	*15.1%*
Age 3 to 16 yrs	558,615	*86.5%*	815,910	*86.0%*	1,099,544	*85.2%*	1,317,388	*85.6%*	1,474,515	*80.3%*	1,216,895	*81.6%*	751,538	*83.4%*	673,218	*83.6%*	844,304	*82.6%*	973,041	*82.8%*	938,984	*83.2%*	10,663,954	*83.4%*
COLYTE & GEN	**7,442**	***1.1%***	**7,582**	***0.8%***	**6,568**	***0.5%***	**5,185**	***0.3%***	**5,610**	***0.3%***	**5,501**	***0.4%***	**4,760**	***0.5%***	**5,746**	***0.7%***	**3,421**	***0.3%***	**2,714**	***0.2%***	**1,996**	***0.2%***	**56,526**	***0.4%***
Age <1	62	*0.8%*	147	*1.9%*	68	*1.0%*	76	*1.5%*	59	*1.0%*	37	*0.7%*	22	*0.5%*	29	*0.5%*	35	*1.0%*	44	*1.6%*	23	*1.2%*	603	*1.1%*
Age 1 to 2 yrs	656	*8.8%*	414	*5.5%*	201	*3.1%*	155	*3.0%*	185	*3.3%*	242	*4.4%*	270	*5.7%*	327	*5.7%*	83	*2.4%*	66	*2.4%*	39	*2.0%*	2,637	*4.7%*
Age 3 to 16 yrs	6,724	*90.4%*	7,021	*92.6%*	6,299	*95.9%*	4,954	*95.5%*	5,367	*95.7%*	5,222	*94.9%*	4,468	*93.9%*	5,390	*93.8%*	3,302	*96.5%*	2,604	*96.0%*	1,934	*96.9%*	53,286	*94.3%*
HALFLYTELY & GEN					**238**	***0.0%***	**2,002**	***0.1%***	**2,882**	***0.2%***	**3,267**	***0.2%***	**3,686**	***0.4%***	**3,950**	***0.5%***	**4,085**	***0.4%***	**2,688**	***0.2%***	**2,203**	***0.2%***	**25,000**	***0.2%***
Age <1					4	*1.7%*	36	*1.8%*	42	*1.5%*	30	*0.9%*	25	*0.7%*	35	*0.9%*	38	*0.9%*	20	*0.7%*	13	*0.6%*	244	*1.0%*
Age 1 to 2 yrs					13	*5.5%*	42	*2.1%*	67	*2.3%*	113	*3.5%*	70	*1.9%*	59	*1.5%*	50	*1.2%*	15	*0.6%*	23	*1.0%*	452	*1.8%*
Age 3 to 16 yrs					221	*92.9%*	1,924	*96.1%*	2,772	*96.2%*	3,123	*95.6%*	3,591	*97.4%*	3,855	*97.6%*	3,997	*97.8%*	2,654	*98.7%*	2,166	*98.4%*	24,304	*97.2%*
NULYTELY & GEN	**5,042**	***0.8%***	**4,756**	***0.5%***	**4,011**	***0.3%***	**3,177**	***0.2%***	**3,127**	***0.2%***	**3,219**	***0.2%***	**3,023**	***0.3%***	**3,201**	***0.4%***	**1,963**	***0.2%***	**1,941**	***0.2%***	**1,713**	***0.1%***	**35,173**	***0.3%***
Age <1	82	*1.6%*	113	*2.4%*	75	*1.9%*	60	*1.9%*	42	*1.3%*	29	*0.9%*	22	*0.7%*	48	*1.5%*	34	*1.7%*	36	*1.9%*	30	*1.8%*	571	*1.6%*
Age 1 to 2 yrs	466	*9.2%*	243	*5.1%*	136	*3.4%*	70	*2.2%*	140	*4.5%*	96	*3.0%*	118	*3.9%*	100	*3.1%*	33	*1.7%*	27	*1.4%*	19	*1.1%*	1,447	*4.1%*
Age 3 to 16 yrs	4,494	*89.1%*	4,400	*92.5%*	3,800	*94.7%*	3,047	*95.9%*	2,946	*94.2%*	3,093	*96.1%*	2,883	*95.4%*	3,054	*95.4%*	1,896	*96.6%*	1,878	*96.8%*	1,664	*97.2%*	33,156	*94.3%*
GOLYTELY & GEN	**2,736**	***0.4%***	**1,660**	***0.2%***	**1,273**	***0.1%***	**1,400**	***0.1%***	**1,737**	***0.1%***	**2,111**	***0.1%***	**3,110**	***0.3%***	**3,750**	***0.5%***	**6,585**	***0.6%***	**7,303**	***0.6%***	**7,252**	***0.6%***	**38,917**	***0.3%***
Age <1	25	*0.9%*	14	*0.8%*	12	*0.9%*	6	*0.4%*	6	*0.3%*	5	*0.2%*	16	*0.5%*	22	*0.6%*	40	*0.6%*	67	*0.9%*	41	*0.6%*	254	*0.7%*
Age 1 to 2 yrs	121	*4.4%*	43	*2.6%*	18	*1.4%*	33	*2.4%*	33	*1.9%*	68	*3.2%*	123	*3.9%*	81	*2.2%*	134	*2.0%*	134	*1.8%*	304	*4.2%*	1,093	*2.8%*
Age 3 to 16 yrs	2,590	*94.7%*	1,603	*96.6%*	1,243	*97.6%*	1,361	*97.2%*	1,698	*97.8%*	2,038	*96.5%*	2,971	*95.5%*	3,647	*97.2%*	6,411	*97.4%*	7,101	*97.2%*	6,906	*95.2%*	37,570	*96.5%*
MOVIPREP									**59**	***0.0%***	**731**	***0.0%***	**902**	***0.1%***	**1,271**	***0.2%***	**1,337**	***0.1%***	**1,138**	***0.1%***	**873**	***0.1%***	**6,311**	***0.0%***
Age <1											6	*0.8%*	2	*0.2%*	31	*2.4%*	16	*1.2%*	10	*0.9%*	31	*3.6%*	95	*1.5%*
Age 1 to 2 yrs									1	*2.2%*	11	*1.5%*	41	*4.5%*	34	*2.7%*	27	*2.0%*	27	*2.3%*	14	*1.6%*	154	*2.4%*
Age 3 to 16 yrs									57	*97.8%*	715	*97.7%*	860	*95.3%*	1,207	*94.9%*	1,294	*96.9%*	1,102	*96.8%*	828	*94.8%*	6,063	*96.1%*

Source: IMS Vector One®: National, Years 2002-YTD Oct 2012 Data Extracted Dec 2012. File: VONA 2012-1517 FDA_PEG-3350_PED_Ages_Broken_Out 12-11-12.xls

Figure 3: Nationally estimated number of prescriptions for polyethylene glycol 3350 and generic equivalents dispensed to the *pediatric population* (0-16 years) in U.S. outpatient retail pharmacies, years 2002 - 2011

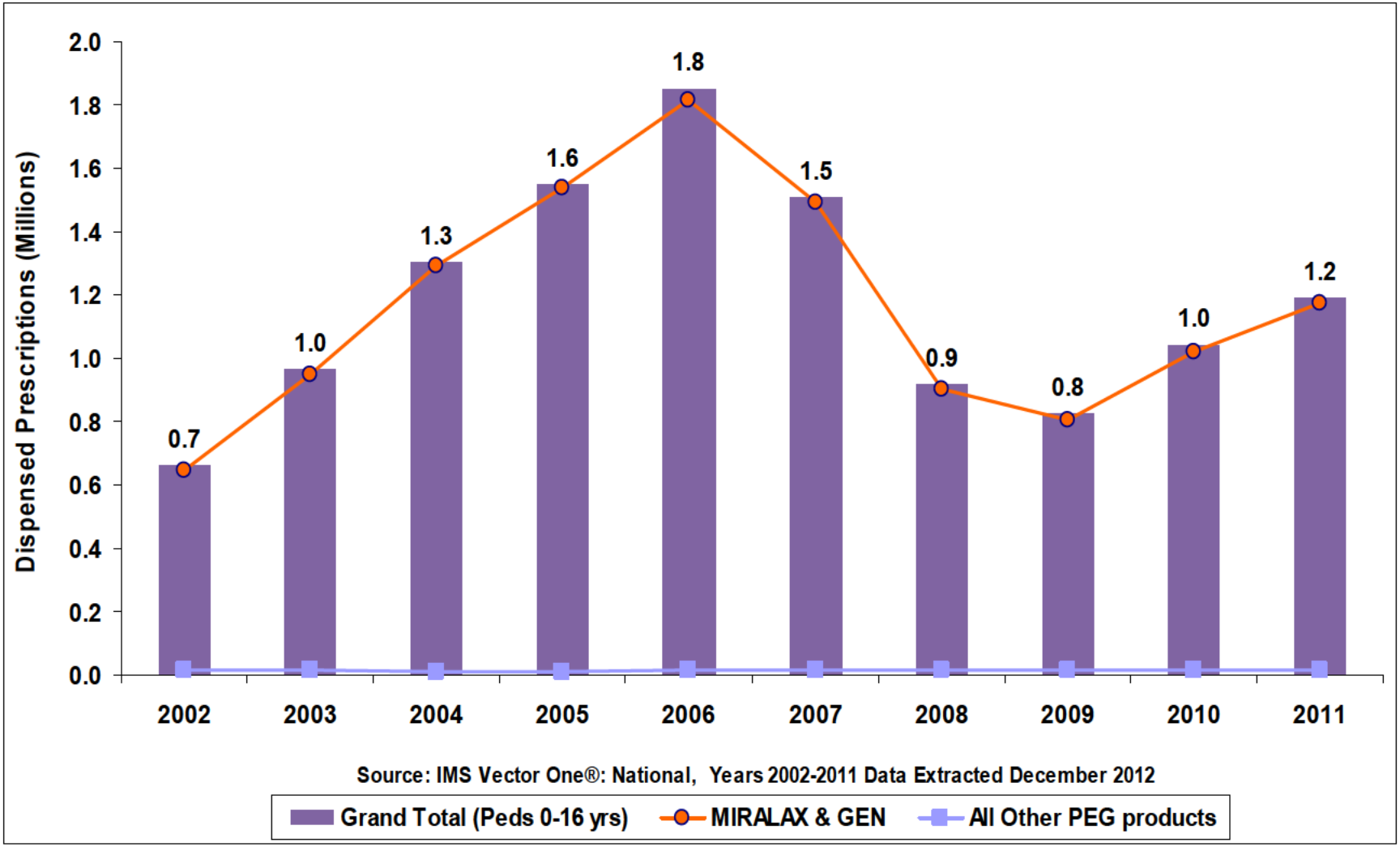

Figure 4: Nationally estimated number of prescriptions for bowel prep polyethylene glycol 3350 products and generic equivalents (excluding MiraLAX and generic equivalents) dispensed to the *pediatric population* (0-16 years) in U.S. outpatient retail pharmacies, years 2002-2011

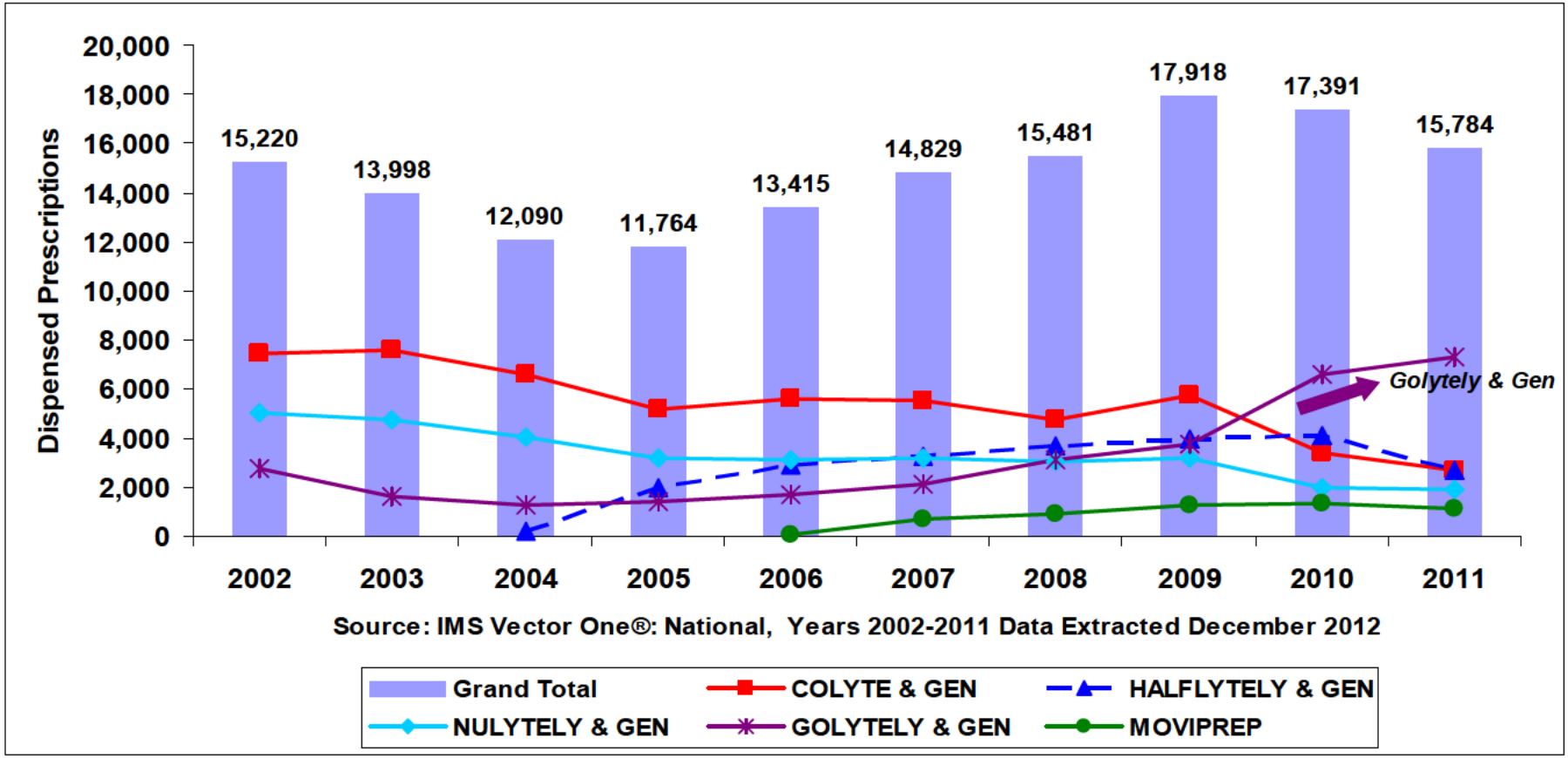

Table 4. Drug use mentions* for laxative products (USC Classes: 56520, 56700, 56900) by patient age, for the top diagnoses associated with use as reported by U.S. office-based physician practices, year 2011

	Year 2011		
	Uses (000)	*Share%*	95% Confidence Interval Uses (000)
Total Market	8,358	*100.0%*	7,926-8,790
<1 year	**30**	***0.4%***	**4-56**
5640 CONSTIPATION	30	*100.0%*	4-56
Miralax	25	*83.7%*	2-49
Lactulose	5	*16.4%*	<0.5-15
1-2 years	**113**	***1.4%***	**63-163**
5640 CONSTIPATION	109	*95.9%*	59-158
Miralax	100	*91.7%*	52-147
Lactulose	9	*8.3%*	<0.5-23
7890 ABDOMINAL PAIN	5	*4.1%*	<0.5-15
Lactulose	5	*100.0%*	<0.5-15
3-16 years	**890**	***10.7%***	**749-1031**
5640 CONSTIPATION	689	*77.4%*	565-813
Miralax	631	*91.6%*	512-750
Glycolax	22	*3.2%*	<0.5-44
Dulcolax	10	*1.5%*	<0.5-25
Golytely	9	*1.3%*	<0.5-23
Dulcolax Balance	6	*0.9%*	<0.5-17
Lactulose	6	*0.8%*	<0.5-17
Polyethylene Glycol	5	*0.7%*	<0.5-15
7890 ABDOMINAL PAIN	127	*14.3%*	74-181
Miralax	120	*94.5%*	68-172
Glycolax	7	*5.5%*	<0.5-20
3077 ENCOPRESIS	38	*4.3%*	9-67
Miralax	38	*100.0%*	9-67
5641 IRRITABLE COLON	10	*1.1%*	<0.5-25
Miralax	10	*100.0%*	<0.5-25
5589 NONINF GASTROENTERIT NEC	7	*0.8%*	<0.5-19
Miralax	7	*100.0%*	<0.5-19
4556 HEMORRHOIDS NOS	5	*0.6%*	<0.5-16
Miralax	5	*100.0%*	<0.5-16
5693 RECTAL & ANAL HEMORRHAGE	5	*0.6%*	<0.5-16
Miralax	5	*100.0%*	<0.5-16
All Others	9	*1.0%*	<0.5-22
17+ years	6,923	*82.8%*	6,530-7,317
5640 CONSTIPATION	1,361	*19.7%*	1,186-1,535
Miralax	920	*67.6%*	776-1,063
Lactulose	137	*10.1%*	82-192
Dulcolax	98	*7.2%*	52-145
Kristalose	46	*3.4%*	14-79
Moviprep	42	*3.1%*	11-73
Polyethylene Glycol	32	*2.4%*	5-59
Golytely	28	*2.0%*	3-52
All Others	57	*4.2%*	21-93
V719 OBSERV-SUSPECT COND NOS	1,062	*15.3%*	908-1,215
Moviprep	341	*32.1%*	253-428
HalfLytely	192	*18.1%*	126-257
Golytely	162	*15.3%*	102-223
Dulcolax	95	*8.9%*	49-141
Miralax	91	*8.6%*	46-136
Suprep	77	*7.3%*	36-119
CoLyte	50	*4.7%*	17-84
All Others	54	*5.1%*	19-89
V765 SCRN MAL NEOP-INTESTINE	509	*7.4%*	403-616
Moviprep	222	*43.6%*	152-293
Golytely	83	*16.3%*	40-126
HalfLytely	59	*11.6%*	23-95
Suprep	47	*9.2%*	14-79
CoLyte	28	*5.6%*	3-54
NuLytely	23	*4.5%*	<0.5-45
Trilyte	15	*3.0%*	<0.5-34
All Others	32	*6.3%*	5-59
V127 HX OF GI DISEASE	494	*7.1%*	389-599
Moviprep	160	*32.4%*	101-220
Suprep	86	*17.4%*	42-130
Golytely	79	*16.0%*	37-121
HalfLytely	51	*10.2%*	17-84
Miralax	44	*9.0%*	13-76
Dulcolax	28	*5.6%*	3-53
NuLytely	22	*4.5%*	<0.5-44
All Others	24	*4.9%*	1-47
All Other Diagnoses	3,498	*50.5%*	2,996-4,001
Unspecified Age	400	*4.8%*	306-495

Source: Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel, Year 2011. Extracted Oct2012.

* The term "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

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12/31/2012

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01/02/2013

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

PATIENT LABELING REVIEW

Date:	December 14, 2012
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	Suclear (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution)
Dosage Form and Route:	oral solution and powder for oral solution
Application Type/Number:	NDA 203-595
Applicant:	Braintree Laboratories, Inc.

1 INTRODUCTION

On December 19, 2011, Braintree Laboratories, Inc. submitted for the Agency's review New Drug Application (NDA) 203-595 for Suclear (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution) with the proposed indication for cleansing of the colon as a preparation for colonoscopy in adults. On March 1, 2012, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Instructions for Use (IFU) for Suclear (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution).

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Instructions for Use (IFU) for Suclear.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 14, 2012, and a revised review of the IFU was sent to DGIEP on December 4, 2012.

DMPP conferred with the Division of Consumer Drug Promotion (DCDP), Office of Prescription Drug Promotion (OPDP) and a separate OPDP review of the IFU was completed on November 7, 2012.

2 MATERIAL REVIEWED

- Draft Suclear (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution) IFU received on December 19, 2011, and received by DMPP on March 1, 2012.
- Draft Suclear (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution) Prescribing Information (PI) received on December 19, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2012.
- Division of Medication Error, Prevention, and Analysis (DMEPA) Suclear Label, Labeling, and Packaging Review dated September 14, 2012 and revised review dated December 4, 2012.
- Division of Consumer Drug Promotion (DCDP), Office of Prescription Drug Promotion (OPDP) review of Suclear Consult Review dated November 7, 2012.

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 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th 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 have reformatted the IFU document using the Verdana font, size 11.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
12/14/2012

BARBARA A FULLER
12/14/2012

LASHAWN M GRIFFITHS
12/14/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion

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

Memorandum

Date: November 7, 2012

To: Matthew Scherer, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Kendra Y. Jones, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 203595 - OPDP labeling comments for Suclear

OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, carton, instructions for use (IFU), and the IFU booklet for Suclear, NDA 203595, submitted for consult on September 4, 2012, and offers the following comments.

PI and Medication Guide
OPDP's comments on the PI and Medication Guide are provided directly in the marked-up document below.

Proposed IFU, IFU booklet and carton
Provided below are the proposed instructions for use and the mock-up versions of the proposed carton and IFU booklet. OPDP's comments on the proposed IFU are provided directly in the marked-up document below. Because the marked-up IFU and the proposed mock-up versions of the carton and IFU booklet contain the same IFU information, OPDP will not reiterate our IFU comments on the mock-up versions of the proposed carton and IFU booklet. Comments from the marked-up IFU should be applied to the proposed mock-up versions of the carton and IFU booklet provided below.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding the PI, please contact Katie Klemm at 301-796-3946 or Kathleen.Klemm@fda.hhs.gov.

If you have any questions regarding the Medication Guide, IFU, IFU booklet or carton please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
11/07/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: Oct 19, 2012

From: Erica Radden, M.D.
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Re: Request for PREA waiver

Drug: BLI850 (sodium sulfate, potassium sulfate and magnesium sulfate and PEG-3350 and (b) (4) for Oral Solution) (proposed name: Suclear)

Sponsor: Braintree laboratories, Inc.

Proposed Indication: Gastrointestinal lavage for cleansing of the colon as a preparation for colonoscopy in adults.

Dosage form and Route of administration: One 6 oz bottle of oral solution and one 2 liter bottle with powder for reconstitution

Dosing regimen:
Proposed Adults:

(b) (4)

[redacted]

Application Number: NDA 20-3595

Submission Date: December 16, 2011

Sequence Number: N/A- paper submission

Consult Request: "The sponsor supports its waiver request with the result of a retrospective study of colonoscopy rates in pediatrics. This study was used to support a waiver request for Suprep (NDA 22372). PMHS was consulted (see Laurie Conklin's review dated 3-31-2011 attached to NDA 22372) and recommended the waiver be denied and DGIEP agreed.

DGIEP requests PMHS to consider the appropriateness of these conclusions and the waiver request of BLI850.

Furthermore, BLI850, unlike Suprep, contains polyethylene glycol 3350. We are aware of potentially neurotox-related AEs (e.g., seizures) associated with MiraLax (PEG 3350) in pediatric patients. Please comment on any safety considerations that would impact our assessment of the acceptability of a waiver."

Materials Reviewed:

- Briefing packet (December 16, 2011)
- Proposed BLI850 label (December 16, 2011; revised 10/2011)
- PMHS consult for Suprep dated March 31, 2011 attached to NDA 22-372

- Memorandum of Meeting Minutes Drug Safety Oversight Board Meeting (June 18, 2009)

Background:
Colonoscopy is used in the diagnosis of a variety of gastrointestinal disorders in children and adolescents; most notably, inflammatory bowel disease.[1] It is also used as a therapeutic tool in the treatment of colonic polyps and lower gastrointestinal tract bleeding.[1] Successful performance of colonoscopy is highly dependent on adequate bowel preparation.[1] Agents used in bowel preparation can be categorized as osmotic or stimulants, though some agents exert a combined effect.[1] The most commonly used agents for colonoscopy preparation in adult and pediatric patients include polyethylene glycol (PEG)-3350 solutions, senna, bisacodyl and magnesium salts.

Common adverse effects associated with colonoscopy preparations in adult and pediatric patients include electrolyte abnormalities, dehydration, abdominal pain/cramping, nausea, vomiting and bloating.[1] Additionally, PEG has purportedly been associated with pediatric case reports of metabolic acidosis (with and without increased anion gap), and neuropsychiatric adverse events such as seizures, headache, anxiety, lethargy, sedation, aggression, rages and mood swings.[2]

Of the several approved osmotic bowel preparation agents, all of which include PEG, only two are approved for use in patients older than six months; NuLYTELY and its generic equivalent, TriLYTE, which contain PEG-3350 with electrolytes. Also, the stimulant laxatives that are frequently used for bowel preparation in children (senna, bisacodyl and magnesium sulfate) are approved under OTC monograph for relief of occasional constipation (irregularity), but not bowel cleansing. Similarly, while MiraLax (PEG-3350) is an OTC osmotic laxative that is frequently used in pediatric patients for relief of occasional constipation and bowel preparation, approval has not been granted for MiraLax in children less than 17 years of age.

Reviewer comment: The currently marketed OTC formulation of MiraLax was approved in 2006 and the previous prescription formulation that was approved in 1999 (prior to PREA) was discontinued. The OTC indication is not considered a new indication and since there was no new ingredient, dosage form, dosing regimen or route of administration PREA was not triggered with the 2006 approval. Therefore, the OTC formulation of MiraLax does not have a PREA PMR. It should be noted that the approval letter for the OTC formulation of MiraLax includes a PREA PMR but this is incorrect.

PREA required studies for colonoscopy preparation were waived with the 2006 approval of Moviprep, which also contains PEG. However, more recently, FDA's opinion on the need to require pediatric studies for colonoscopy has changed. Several bowel preparation products have been approved in adults and have pending PREA PMRs (e.g.

[1] Hunter A, Mamula P. Bowel preparation for pediatric colonoscopy procedures. *JPGN*. Sep 2010;51(3):254-61.
[2] Memorandum of Meeting Minutes Drug Safety Oversight Board Meeting (June 18, 2009)

SUPREP, PICOPREP, and HalfLytely with Bisacodyl). The sponsor for HalfLytely with Bisacodyl has completed one PREA PMR in patients age 6-(b)(4) years old to evaluate safety and efficacy compared to NuLytely which found no new safety signals[3]. PICOPREP, which does not contain PEG was discussed at the Pediatric Review Committee (PeRC) in May 2012 during which a plan to waive studies in infants under (b)(4) of age and defer study requirements for pediatric patients age (b)(4) and older was agreed upon.

Regulatory Background:

On December 16, 2011, Braintree submitted a new NDA for BLI850, an osmotic agent containing a combination of sulfate salts, PEG-3350 and electrolytes with the proposed indication of bowel preparation prior to colonoscopy. The application includes a request for a waiver of PREA studies for (b)(4) pediatric ages. The sponsor believes that BLI850 (b)(4) In support of this waiver request, the sponsor has submitted the results of an epidemiology study that was completed as one of the postmarketing requirements under PREA for SUPREP, another bowel preparation that is also sponsored by Braintree.

This epidemiology study was originally submitted to the FDA in November 2010 to support a (b)(4) waiver request for SUPREP and release the sponsor from their additional PREA study requirements to perform dose ranging studies comparing safety and efficacy of SUPREP to NuLYTELY for patients age 0-16 years. PMHS completed a consult from DGIEP in March 2011 to assess the acceptability of the sponsor's justification for this request. PMHS concluded that a (b)(4) waiver was not appropriate (b)(4) this justification did not meet the criteria for a waiver. Although a recommendation to deny the request for a (b)(4) waiver was made, a (b)(4) was believed to be reasonable since bowel preparation in infants can be achieved solely with the administration of clear fluids for 24 hours. (See the March 31, 2011 PMHS consult on SUPREP, NDA 22-372, for a detailed discussion on the sponsor's waiver request). The Division concurred with this recommendation, along with the Pediatric Review Committee (PeRC), and denied the request for a (b)(4) waiver for SUPREP. (b)(4) . However, DGIEP presented information at the PeRC meeting on August 1, 2012 for BLI850 that bowel preparation could be achieved in

[3] Action Summary Review by Donna Griebel for NDA 21-551/S013 (July 16, 2010)
[4] FDA Guidance for Industry. Pediatric Studies: How to Comply with the Pediatric Research Equity Act, Title IV of the Food and Drug Administration Amendments Act of 2007. Section VB.

infants up to one year of age with clear fluids and recommended a partial waiver in infants less than one year of age with which the PeRC agreed.

Comments on Safety of PEG:

PEG is generally believed to be safe since it is minimally absorbed.[1,5] However, case reports of metabolic acidosis and neuropsychiatric adverse events associated with the use of PEG products prompted a Drug Safety Oversight Board (DSB) on June 18, 2009. The presentation to the board included a description of the adverse events, along with a safety review of the published literature, information on practice guidelines, and a review of the non-clinical and pharmacokinetic data on PEG. [See the PMHS consult dated May 20, 2009 related to the safety of PEG use in pediatric patients, for a detailed discussion on the literature review (Safety report #566).] The literature review did not identify clinically significant electrolyte or neurologic problems in pediatric patients taking PEG. In addition, a clinical practice guideline (CPG) discussing treatment of constipation created by the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and two clinical references (the Harriet Lane Handbook and Up-to Date) recommend the use of PEG in children. The CPG does, however, recommend safety studies be performed before widespread use in infants is advised.

Discussion at the DSB centered on the following points:

- Metabolic acidosis appears to be associated with lower molecular weight PEGs such as (b) (4) and (b) (4).
- (b) (4) and (b) (4) are more readily absorbed than higher molecular weight PEG (b) (4)
- A wide variability in systemic absorption of PEG was also noted in adults and children.
- There are gaps in the knowledge of the molecular weight distribution of PEG products, long term stability of PEG-3350, and systemic exposure of PEG in patients with GI lesions or children with constipation

The Board was split as to whether the 25 reports of neuropsychiatric events represented a safety signal as all the reports were classified as consumer reports and none were verified by health care professionals; several board members advised caution with interpreting any potential safety signal from consumer reports of adverse events when healthcare professionals had not also reported the adverse event. Furthermore, these reports were mostly noted in patients taking MiraLax (14/25) primarily for constipation with the majority of reports (16/25) noting use for over a month. Four adverse events involving metabolic acidosis were reported. The minutes did not mention any use of PEG products for bowel preparation. There was no consensus on recommended labeling changes in the absence of additional data, however, areas warranting further study were proposed such as safety of one-time vs. chronic use, assessment of associated metabolic or neuropsychiatric safety signals, characterization of the molecular weights comprising

[5] Pelham RW, Nix LC, Chavira RE, Cleveland MV and Stetson P. Clinical trial: single- and multiple-dose pharmacokinetics of polyethylene glycol (PEG-3350) in healthy young and elderly subjects. *Alimentary Pharmacology and Therapeutics*. 2008;28(2):256-265

PEG products, and evaluation of the 20-40 fold variability in absorption seen between patients

Of note, a Citizen Petition has been submitted to the Agency by the Empire State Consumer Project, requesting a review of the safety issues surrounding PEG use. Thus far, a safety concern has not been identified that would preclude pediatric studies for PEG, information from which would be of particular interest given its widespread use. The DSB on PEG products reviewed reports that mostly involved chronic MiraLax use for the treatment of constipation. None of the case reports involved MiraLax use as a bowel preparation for colonoscopy in which much larger doses may be administered albeit for one-time use. However, three cases noted use of larger volume PEG solutions (2400mL per NG tube, 1 gallon orally and 20mL/kg/hr per NG tube) over 24 hours or less that were associated with metabolic acidosis. Thus, studies are needed to evaluate the safety of larger dose administration of PEG in one-time bowel cleaning regimens, as well as smaller doses of OTC PEG-3350 which are often used chronically to treat constipation.

The following table shows a comparison of PEG products and recommended dosing:

Product	PEG content	Indication	Pediatric dosing	Max dose
PEG-3350		Constipation-disimpaction	1-1.5g/kg/day[1]	17g/day (adults)
		Constipation-maintenance	1g/kg/day[1]	
		Bowel prep	1.25mg/kg/day over 4 days[2]	
NuLYTELY	105g/L	Bowel prep	25ml/kg/hour (2.625g/kg/hr) until rectal effluent is clear[3]	420g in 4L
BLI850	105g/L	Bowel prep	N/A	210g in 2L
HalfLytely	105g/L	Bowel prep	N/A	210g in 2L
Moviprep	2 pouches with 100g in each	Bowel prep	N/A	200g in 2L

[1] NASPGHAN guideline recommendations
[2] National Guideline Clearinghouse recommendations
[3]Per labeling

Discussion and Conclusions:
The sponsor presents a justification for a (b) (4) waiver identical to that submitted for SUPREP asserting that (b) (4) As noted in the previous PMHS recommendations regarding SUPREP (See the March 31, 2011 PMHS consult on SUPREP, NDA 22-372 for a

detailed discussion on the sponsor's waiver request), both of these conditions must be met in order for a waiver to be granted on this criterion. PMHS believes that sufficient evidence has not been provided to support either component of this reason for a waiver.

The sponsor believes that BLI850 does not offer a meaningful benefit over NuLYTELY because NuLYTELY is an electrolyte balanced solution that requires no supplemental water intake and is approved for children ages 6 months and older. However, NuLYTELY only offers a one day dosing regimen whereas BLI850 offers a split dosing regimen. Therefore, use of BLI850 may provide a meaningful benefit for two reasons: (1) improved compliance in children by limiting the volume they would need to ingest at one sitting and (2) the total fluid intake is less for either the same day or split dosing regimen compared to NuLYTELY as the total volume supplied for NuLYTELY is 4 liters (135 oz) vs. BLI850 in which the total volume is 3.4 liters (115.6 oz).

Also, as with SUPREP, (b) (4)

Under PREA, a waiver may also be granted for one of the following reasons:

(1) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).

Reviewer comment: The reviewer notes that studies could be performed at large pediatric medical centers. The sponsor for HalfLytely has completed a study in patients age 6- (b) (4) evaluating safety and efficacy compared to NuLYTELY to fulfill PREA PMRs. In addition, MiraLax and HalfLytely have pending PREA PMRs. Therefore, the reviewer does not believe that the sponsor could qualify for a waiver based on this criterion.

(2) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included labeling.

Reviewer comment: The reviewer notes that there are multiple studies which suggest that PEG with electrolytes may be efficacious for pediatric colonoscopy preparation.[1] Also, there are recommendations for the use of MiraLax in bowel preparation for pediatric patients by the National Guideline Clearinghouse.[4] Therefore, there is no evidence the product would be ineffective. With respect to safety, dehydration and electrolyte changes are well-known possible adverse events with bowel preps. Despite the absence of reports of these adverse events in the literature, there are adverse event reports of metabolic acidosis and neuropsychiatric events associated with PEG use in pediatric patients, However, review of safety reports related to PEG use at the 2009 DSMB did not prompt any additional warnings in labeling for pediatric patients. The sponsor has not submitted any evidence that this product has a different safety profile to other bowel preparations containing PEG with electrolytes. Presuming DGIEP does not identify any

[1] Hunter A, Mamula P. Bowel preparation for pediatric colonoscopy procedures. JPGN 2010; 51:254-61.
[4] A consensus document on bowel preparation before colonoscopy (2011) National Guideline Clearinghouse. http://www.guideline.gov/content.aspx?id=9619

safety or efficacy concerns in adults, pediatric studies can proceed as long as appropriate monitoring for these events are incorporated into clinical studies. PEG products are currently in widespread use and supported by clinical practice guidelines and pediatric references for colonoscopy preparation.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Reviewer comment: Since this formulation is similar to currently approved bowel preparations for children, such as NuLYTELY and TriLYTE, this also would not apply.

Recommendations:
PMHS recommends that a (b) (4) pediatric waiver should be denied. However, a partial waiver for patients under one year would be reasonable since bowel preparation can be accomplished by administration of clear fluids in infants pre-colonoscopy for a minimum of 24 hours. A partial waiver in this age group would be consistent with other recently approved products such as SUPREP and HalfLytely. Additionally, the Division should consider requesting pharmacokinetic assessments with the studies required for the pediatric study plan. In particular, systemic exposure of sulfate, PEG and other small molecules such as (b) (4) as well as electrolytes should be assessed. Finally, staggered enrollment of pediatric cohorts with adolescents first, then older children and lastly younger children is suggested.

Due to the expected risks of dehydration and electrolyte abnormalities, appropriate monitoring of vital signs, fluid status and electrolytes will need to be included in the studies. Although PMHS acknowledges that evaluating neuropsychiatric adverse events in the colonoscopy preparation population may be problematic due to concomitant use of sedatives and anesthetic agents, an evaluation of neuropsychiatric adverse events should also be included in the studies.

Review of labeling:
Current proposed labeling dated March 5, 2012:

> **8.4 Pediatric Use**
> Safety and effectiveness in pediatric patients have not been established.

Labeling Recommendations:
If a partial waiver is granted because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of patients in the pediatric age group(s) for which the waiver is being requested or the studies are deferred, then the current proposed language for the Pediatric Use subsection is appropriate. However, if a waiver for any pediatric age group is granted due to safety concerns then section 8.4 must include a description of the specific safety concern.

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/s/

ERICA D RADDEN
10/19/2012

HARI C SACHS
10/19/2012
I agree with these recommendations

LYNNE P YAO
10/22/2012

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

PATIENT LABELING REVIEW

Date:	October 2, 2012
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Suclear (sodium sulfate, potassium sulfate, magnesium sulfate) oral solution and (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride) powder for oral solution
Dosage Form and Route:	oral solution and powder for oral solution
Application Type/Number:	NDA 203-595
Applicant:	Braintree Laboratories, Inc.

1 INTRODUCTION

On December 19, 2011, Braintree Laboratories, Inc. submitted for the Agency's review New Drug Application (NDA) 203-595 for Suclear (sodium sulfate, potassium sulfate, magnesium sulfate) oral solution and (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride) powder for oral solution with the proposed indication for cleansing of the colon as a preparation for colonoscopy in adults. On March 1, 2012, the the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Suclear (sodium sulfate, potassium sulfate, magnesium sulfate) oral solution and (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride) powder for oral solution.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Medication Guide (MG) for Suclear.

2 MATERIAL REVIEWED

- Draft Suclear (sodium sulfate, potassium sulfate, magnesium sulfate) oral solution and (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride) powder for oral solution MG received on December 19, 2011, and received by DMPP on March 1, 2012.
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- Division of Medication Error Prevention and Analysis (DMEPA) Review of Suclear Label, Labeling and Packaging Review dated September 14, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th 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 have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

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/s/

KAREN M DOWDY
10/02/2012

BARBARA A FULLER
10/02/2012

LASHAWN M GRIFFITHS
10/02/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	September 14, 2012
Reviewer:	Teresa McMillan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh. Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh. Division of Medication Error Prevention and Analysis
Drug Name(s):	Suclear (Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate) Oral Solution and (PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride) for Oral Solution
Strengths:	17.5 g/3.13 g/1.6 g and 210 g/2.86 g/5.6 g/ (b) (4)
Application Type/Number:	NDA 203595
Applicant/Sponsor:	Braintree Laboratories, Inc.
OSE RCM #:	2012-461

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, Prescribing Information, Medication Guide, mixing cup, and reconstitution container for Suclear (Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate) Oral Solution and (PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride) for Oral Solution, NDA 203595 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On June 22, 2012, Braintree Laboratories, Inc. submitted a request to the Agency for an assessment of the proposed proprietary name, Suclear which is currently being evaluated in a separate review (OSE# 2012-1459). Additionally, the Applicant submitted the associated labels and labeling for the proposed product on June 22, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 22, 2012 proprietary name submission.

- Active Ingredients: Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate and PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride
- Indication of Use: Cleansing of colon as a preparation for colonoscopy in adults
- Route of Administration: Oral
- Dosage Form: Oral solution and powder for reconstitution
- Strength: 17.5 g/3.13 g/1.6 g and 210 g/2.86 g/5.6 g/ (b) (4)
- Dose and Frequency: Dilute solution so that it equals 16 ounces and drink over two hours then dissolve powder in 2 liter jug with water and consume over two hours. Two step process can be completed as a two day regimen or one day regimen
- How Supplied: Kit containing one 6 ounce bottle of oral solution, one 16 ounce mixing container, one 2 Liter bottle with powder for reconstitution
- Storage: 20° to 25° C (68° to 77°

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels, Carton Labeling, Prescribing Information, Medication Guide, the mixing cup and the reconstitution container submitted on June 22, 2012 (See Appendices A, B, C, and D for images, no image for Prescribing Information and Medication Guide)

3 MEDICATION ERROR RISK ASSESMENT

The proposed product is designed as a kit to administer two different oral solutions containing electrolytes or PEG-3350 and electrolytes. The Applicant refers to the different oral solutions as Dose 1 and Dose 2. The dosing regimen can be administered over 1 or 2 days. The kit contains a 6 ounce bottle of oral solution (Dose 1) and a 2 liter bottle for oral solution (Dose 2), and 16 ounce opaque mixing container that can be utilized for administration of Dose 1 and 2. This type of two-step dosing regimen is not commonplace. Most products in this class of drugs are mixed in a single bottle and administered over the course of a day prior to the procedure. However, this product requires the patient or caregiver to prepare two different solutions in two different containers. Additionally, the two-step dosing regimen contains different active ingredients. Approving the entire product to be administered as a split-dose (2-day) regimen or as a (b) (4) (1-day) regimen increases the probability that the instructions for use could be confused and result in errors. Thus, to help mitigate potential confusion the label and labeling need to be as concise and clear as possible.

The mixing cup is used for mixing and administration. The cup is opaque and at the top of the cup the following statements appear between two horizontal lines: "16-oz. Fill Line" (b) (4) Although, there are arrows which point to a fill line that appear above each statement and under the lid of the cup, the arrows, the statements, the fill line, and the lid of the cup are all opaque and thus hard to read because there is insufficient color contrast. Additionally, the placement of these statements between the horizontal lines is confusing because it is difficult to tell if the bottom line is the fill line or the top line is the fill line. To add to the confusion a small opaque fill line appears right below the upper horizontal line. This design could confuse the user and lead them to fill the cup to the incorrect water level. The cup statements and fill line should be more prominent and provide a better contrast against the background.

Furthermore, we note that the Patient Instructions for Use Booklet is designed so that the end user must read the sequential instructions from left to right on one page then continuing from left to right to the next page. Most people read from left to right and top to bottom one page at a time. Since the information is presented in a manner outside of the norm, it may be read out of sequence and lead to confusion. We also note that the

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

established name is incorrect. This product consists of an oral solution and a for oral solution which requires reconstitution. The Applicant presents the established name as a [redacted] (b) (4) Additionally, for the for oral solution portion of this product the Applicant uses the term [redacted] (b) (4) and does not specify the individual electrolyte components of this product. Thus we recommend revisions to address this concern.

We also provide recommendations for the product design, and the labels and labeling in Section 4 to address these deficiencies and clarify information on the labels and labeling to minimize the risk of medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the product design and labels and labeling can be improved to increase the readability and prominence of important information to ensure safe use of the product. DMEPA recommends the following be implemented prior to approval of this NDA:

A. **General Comment**

Present the established name wherever presented on the labels and labeling as the following:

(Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate) Oral Solution and (PEG-3350 and [redacted] (b) (4) for Oral Solution

B. **Mixing Cup**

1. The following statement is not legible because it appears in a clear font against a clear background on the cup: “16-oz. Fill Line”. Revise this statement so that there is sufficient color contrast against the clear background or redesign so that the lettering and the fill line are prominent and can be read.
2. The fill line instruction appears between two horizontal lines. Although, there are arrows pointing to the fill line, this line is thin and opaque, thus making the line virtually illegible on the cup. Also, the top line is thick and the user may confuse the two lines and fill the product to the incorrect line. Revise the cup and consider using a transparent non-indented mixing cup so that a 16 oz. fill line can be easily seen and read by the end user.
3. Delete the following statement: [redacted] (b) (4) because the statement is misleading. The patient must drink an electrolyte solution and water.
4. Add the proprietary name for this product to the mixing cup so that it is identified for use with this product.

C. **Reconstitution Container**

1. The fill line is not recognizable because it is not prominent. Increase the prominence of the fill line so that it is more recognizable.
2. The "Fill Line" statement is not legible because it appears in a clear font against a clear background on the bottle and lacks prominence. Revise this statement so that there is sufficient color contrast against the clear background.

D. **All Labels and Labeling**

The 16 oz. mixing device is identified as a cup and or a container throughout the labels and labeling. For consistency and to avoid confusion, select only one term to represent the 16 oz. device when referenced throughout the labels and labeling.

E. **Prescribing Information**

1. Dosage and Administration (Highlights and Full Prescribing Information):
   a) To maintain consistency of the presentation of information throughout the Prescribing Information add the following statements to appear before the "Add water to the 2 liter fill line on the jug" statement in the Split Dose (2 -day) and the (b) (4) (1-Day) Regimens:

      Optional-Add 1 flavor pack of choice to the 2 liter bottle. Solution can be used with or without flavor packs.

   b) The word ounce and the abbreviation for ounce (oz) both appear in the "Drink all the solution at a rate of 16 oz ounces every 20 minutes" sentence in the Split Dose (2-Day) Regimen section. To avoid confusion, delete the abbreviation for ounce in this sentence.
2. How Supplied/Storage and Handling:

   List the optional Flavor Pack Flavors under the "Each Suclear kit contains" subheading because they are supplied in the kit.
3. Patient Instructions for Use Booklet:
   a) The information on Pages 2 and 3 of the Patient Instructions for Use Booklet does not read in sequential order in the usual reading format from top to bottom from one page to the next. As currently presented, the information can be read out of sequence and lead to confusion. Present the Patient Instructions for Use on pages 2 and 3 in sequential order from top to bottom on one page and then continue in sequential order from top to bottom on the next page.
   b) Remove the (b) (4) from the Patient Instructions For Use handbook because this information is written for healthcare practitioners.

c) Remove the statement [redacted] (b) (4) from the cover of the Patient Instructions for Use Booklet because this information is written for healthcare practitioners.

d) Pages 2 and 3 use a lime green color against a white background to highlight certain terms under the following headings: "What to eat and drink on the day before your procedure" and "Any of the following clear liquids are okay to drink". As presented these terms are not distinctly visible. Provide a better contrast in color to highlight these terms.

F. **Carton Labeling**

1. Include the product strength on the principal display panel of the carton labeling. For example under the "Dose 1" heading on the principal display panel state the following:

   One 6 ounce (177 mL) bottle of Sodium Sulfate 17.5 g, Potassium Sulfate 3.13 g, and Magnesium Sulfate 1.6 g Oral Solution

   For example under the "Dose 2" heading on the principal display panel present as the following:

   One 2-liter bottle of PEG-3350 210 g, Sodium Bicarbonate 2.86 g, Sodium Chloride 5.6 g, and Potassium Chloride 0.74 g for Oral Solution

2. Remove the [redacted] (b) (4) which appear in the proprietary name.
3. Replace the name [redacted] (b) (4) that appears on the top opening of the carton with the approved proposed proprietary name.
4. Remove the number "1" wherever it appears on the principal display panel under the heading "This Carton Contains" and replace it with the word "one". The placement of two numbers next to each other, even with the use of highlighting one of the numbers, as presented in this case, may be confusing because a patient or healthcare practitioner may misinterpret this presentation as '16 ounce', '116 ounce', or '12 liters'.
5. Revise the statement [redacted] (b) (4) on the principal display panel to state the following:

   Full Prescribing Information and One Patient Instruction Booklet with the Medication Guide

6. Increase the prominence of the following statement which appears on the Principal display panel: "Dispense the enclosed Medication Guide to each patient".
7. Increase the prominence of the following statement which appears on the Principal display panel: "NOTE: both doses are required for a complete prep" to be commensurate to the statement "Dilute As Directed Prior to Use" and relocate to appear above the storage statement.

G. **Container Labels**

1. Increase the prominence of the "For use with Suclear kit only" statement on the "Dose 1" and "Dose 2" container labels. Additionally relocate the statement to appear above the "Dose 1" and "Dose 2" statements.
2. Revise the (b) (4) statement that appears on the "Dose 1' and 'Dose 2" container labels to state the following:

   "See complete instructions in the enclosed booklet or on the box before using."
3. Revise the directions on the "Dose 2" container label to state the following:

   "Add 1 flavor pack. Add drinking water to the top of the fill line on the bottle. Shake. Drink one (16 oz.) glass of solution every 20 minutes. Drink all the solution."
4. Delete the (b) (4) statement that appears after the strength on the "Dose 2" container label because this information is redundant and is presented elsewhere on the label.

If you have further questions or need clarifications, please contact Nitin Patel, project manager, at 301-796-5412.

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

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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.

/s/

TERESA S MCMILLAN
09/14/2012

LUBNA A MERCHANT
09/14/2012

SCOTT M DALLAS
09/14/2012

CAROL A HOLQUIST
09/14/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 6, 2012

TO: Matthew Scherer, Regulatory Project Manager
Helen Sile, Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.,
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-595

APPLICANT: Braintree Laboratories, Inc.
DRUG: BLI850 (b) (4) Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate
Oral Solution and PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride for Oral Solution)

NME: No
THERAPEUTIC CLASSIFICATION: Standard
INDICATIONS: Bowel Cleansing Preparation

CONSULTATION REQUEST DATE: April 3, 20123
INSPECTION SUMMARY GOAL DATE: August 17, 2012
DIVISION ACTION GOAL DATE: October 19, 2012
PDUFA DATE: October 19, 2012

I. BACKGROUND:

The sponsor, Braintree Laboratories, Inc. submitted an NDA for the product BLI850 (Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate Oral Solution and PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride for Oral Solution) with the indication of cleansing of the colon in preparation for colonoscopy in adults. During screening procedures for colorectal cancer (CRC), such as sigmoidoscopy, colonoscopy and radiography, it is important that the colon be thoroughly purged and cleansed as much as possible from fecal matter and fluids to permit adequate visualization of the mucosa. Preparations for that purpose, such as NuLytely® and Trilyte®, are isotonic, requiring the patient to ingest significant volumes, about 8 ounces every ten minutes up to a gallon. To improve patient compliance, HalfLytely® and bisacodyl tablet were introduced which resulted in using only 2 liters of the isotonic solution. However, the bisacodyl component has been associated in some patients with abdominal cramping. Moreover, time is lost as the solution is taken after a bowel movement (6 hours maximum). Sodium phosphate based bowel preparations may produce clinically significant fluid or electrolyte shifts.

Previous studies have shown that stool output of 2400 g or greater with percent solids of less than 3% is consistent with adequate cleansing. Various sulfate formulations were attempted but, only those that provided 250 mM or more of sulfate ion induced about 2400 g of stools. The sulfate solutions did not appear to affect serum electrolytes or osmolarity

Two protocols were submitted in support of this application:

1. Protocol BLI850-301: “A Safety and Efficacy Evaluation of BLI850 vs. HalfLytely® and Bisacodyl Bowel Prep Kit as Bowel Cleansing Preparations in Adult Subjects”

2. Protocol BLI850-302: “A Safety and Efficacy Evaluation of BLI850 vs. MoviPrep® as Bowel Cleansing Preparations in Adult Subjects”

The consult identified four sites for inspection, two for each protocol, based on evaluation of site specific efficacy.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects and Site #	Inspection Date	Final Classification
Bal Raj Bhandari, M.D. 608 Grammont St., Monroe, LA 71201	BLI850-301 49 Subjects Site #2	July 9-12, 2012	NAI
Michael Schwartz, D.O. 875 Military Trail, Ste. 210 Jupiter, FL 33458	BLI850-301 58 Subjects Site #9	July 2-12, 2012	NAI
Steven Duckor, M.D. 2617 E. Chapman Ave Orange, CA 92869	BLI850-302 61 Subjects Site #23	July 5-10, 2012	NAI
Dennis Riff, M.D. 1211 W. La Palma Ave Anaheim, CA 92801	BLI850-302 65 Subjects Site #25	June 29-July 9, 2012	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data 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. **Bal Raj Bhandari, M.D.**
   608 Grammont Street
   Monroe, LA 71201

a. **What was inspected:** At this site, 49 subjects were screened and enrolled and 41 subjects completed the study. The field investigators reviewed all 49 subjects' study records including: informed consent, inclusion/exclusion criteria, drug accountability, CRFs , data listings, protocol deviations, safety data, and primary/secondary efficacy parameters.

b. **General observations/commentary:** There was no evidence of underreporting of adverse events or inaccuracy in data capture. The primary endpoint was verified. The inspection did not reveal any federal regulations violations.

c. **Assessment of data integrity:** The data generated at this site are reliable and can be used in support of the NDA.

2. **Michael Schwartz, M.D.**
   875 Military Trail, Suite 210
   Jupiter, FL 33458

a. **What was inspected:** At this site, 58 subjects were screened, 56 subjects enrolled, and 55 subjects completed the study. The field investigator reviewed 30 subjects' records. This included informed consents, inclusion/exclusion criteria, drug accountability records, source data, CRFs, adverse events and efficacy parameters.

b. **General observations/commentary:** There was no evidence of underreporting of adverse events and no discrepancies noted between the source data, eCRFs and the line listings provided to the field investigator. No violations of federal regulations were noted.

c. **Assessment of data integrity:** The data generated from this site are reliable and can be used in support of the NDA.

3. **Steven Duckor, M.D,**
   2617 E. Chapman Ave., Suite 302, Orange, CA 92869

a. **What was inspected:** At this site, 60 subjects were screened, one subject was a screen failure, and 59 subjects completed the study. The field investigator reviewed the records of 30 subjects. This included informed consents, medical history, progress notes, colonoscopy and laboratory reports and adverse events.

b. **General observations/commentary:** There was no evidence of underreporting of adverse events and no discrepancies noted between the source data, eCRFs and the line listings provided to the field investigator. No violations of federal regulations were observed.

c. **Assessment of data integrity:** The data generated at this site are reliable and can be used in support of the NDA.

4. **Dennis Riff, M.D.**
   1211 W. La Palma Ave., Suite 602
   Anaheim, CA 92801

a. **What was inspected:** The field investigator was able to review the source records of Subjects 1 to 32. This included consent forms, CRFs, inclusion/exclusion criteria, lab reports, concomitant medications, drug accountability records, colonoscopy reports, and financial records. The files of Subjects 33 to 65 had been stored on a truck that was stolen and the records could not be recovered. This was reported to the police, the IRB, and the study subjects. The site was able to provide other files such as laboratory reports and colonoscopy reports from the source documents, and these data

could be verified to be consistent with the data listings submitted to the FDA by the sponsor and were provided to the field investigator.

b. **General Observations/Commentary:** Review of the laboratory tests allowed the FDA field investigator to verify that subjects' tests were completed and that the subjects did not have significant electrolyte abnormalities. The colonoscopy reports were reviewed to determine that the bowel cleansing grade was accurately reported in the case report forms. No violations of federal regulations were observed.

c. **Assessment of Data Integrity:** The data generated at this site are reliable and can be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites, two for each protocol, were inspected for this application. All inspections were classified as No Action Indicated (NAI). No violations were noted and no Form FDA 483 was issued. The data generated at the four inspected sites appear reliable and can be used in support of the NDA.

{See appended electronic signature page}

Khairy W. Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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/s/

KHAIRY W MALEK
09/06/2012

SUSAN LEIBENHAUT
09/06/2012

SUSAN D THOMPSON
09/06/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203595 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: sodium sulfate, potassium sulfate, magnesium sulfate and polyethylene glycol 3350 and (b) (4) Dosage Form: Oral solution Strength: 17.5g, 3.13g, 1.6g, 210g, (b) (4)		
Applicant: Braintree Laboratories, Inc. Agent for Applicant (if applicable):		
Date of Application: 12-16-11 Date of Receipt: 12-19-11 Date clock started after UN: NA		
PDUFA Goal Date: 10-19-12	Action Goal Date (if different):	
Filing Date: 2-17-12	Date of Filing Meeting: 2-2-12	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : 4 (new combination)		
Proposed indication(s)/Proposed change(s): cleansing of the colon in preparation for colonoscopy in adults		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): NA

List referenced IND Number(s): 74808, 102894

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	x			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.				NA
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				NA
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			x	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			x	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			x	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			x	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		x		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: not specified ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	x			Sponsor has requested exclusivity but did not specify the duration.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			x	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☒ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).			x	
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	x			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ English (or translated into English) ☒ pagination ☐ navigable hyperlinks (electronic submissions only) - NA **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			x	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	x			Submitted 1-10-12
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the***	x			

original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	x			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			x	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		x		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	x			(b) (4) waiver requested, however, PREA studies will likely be required for (b) (4) 16 years.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	x			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		x		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		x		Sponsor has been advised to submit a proprietary name for review.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		x		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	x			
Is the PI submitted in PLR format?[4]	x			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?		x		To be sent after filing
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		x		To be sent after filing
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		x		To be sent after filing
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent: Safety Statistics will be consulted after filing to help assess lab values.***	x			
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** comments sent 3-22-07 ***If yes, distribute minutes before filing meeting***	x			Preliminary comments sent, meeting cancelled.

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		x		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-2-12

BLA/NDA/Supp #: NA

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: sodium sulfate, potassium sulfate, magnesium sulfate and polyethylene glycol (PEG) 3350 and (b) (4)

DOSAGE FORM/STRENGTH: Oral solution/17.5g, 3.13g, 1.6g, 210g, (b) (4)

APPLICANT: Braintree Laboratories

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): cleansing of the colon in preparation for colonoscopy in adults.

BACKGROUND: (b) (4) has been developed primarily under IND 102894 and, secondarily, under IND 074808. The drug cleanses the colon with a 2 stage osmotic laxative effect; first through a combination of sulfate salts equivalent to a single dose of Suprep and second, PEG 3350 and electrolytes equivalent to the PEG and electrolytes component of Halflytely.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew Scherer	y
	CPMS/TL:	Wes Ishihara	n
Cross-Discipline Team Leader (CDTL)	Rob Fiorentino		y
Clinical	Reviewer:	Helen Sile	y
	TL:	Rob Fiorentino	y
Clinical Pharmacology	Reviewer:	Sandhya Apparaju	y
	TL:	Sue-Chih Lee	n
Biostatistics	Reviewer:	Wen Jen Chen	y
	TL:	Mike Welch	y
Nonclinical	Reviewer:	Yuk-Chow (Eddie) Ng	y

(Pharmacology/Toxicology)			
	TL:	David Joseph	y
Product Quality (CMC)	Reviewer:	Gene Holbert	y
	TL:	Marie Kowblansky	y
Facility Review/Inspection	Reviewer:	TBD	n
	TL:	TBD	n
OSE/DMEPA (proprietary name)	Reviewer:	TBD	n
	TL:	TBD	n
OSE/DRISK (REMS)	Reviewer:	NA	n
	TL:	NA	n
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	n
	TL:	NA	n
Bioresearch Monitoring (OSI)	Reviewer:	TBD	n
	TL:	TBD	n
Other reviewers	NA		
Other attendees	Nitin Patel, Andrew Mulberg, Joyce Korvick, Kevin Bugin		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable

CLINICAL **Comments**: Will have IR for 74-day letter or earlier	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO to be determined by early March 2012
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**: Will have IR for 74-day letter or earlier	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Will have IR for 74-day letter or earlier	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division level – specific signatory to be determined

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: none

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter.

	☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☒	Other: Issue patient labeling, DDMAC, DRISK, Safety Statistics consults

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MATTHEW C SCHERER
02/17/2012

RICHARD W ISHIHARA
02/17/2012