APPLICATION NUMBER:

209589Orig1s000

OTHER REVIEW(S)
MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 6, 2017
Requesting Office or Division: Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number: NDA 209589
Product Name and Strength: Clenpiq (sodium picosulfate/magnesium oxide/anhydrous citric acid) oral solution, 10 mg/3.5 g/12 g per 160 mL
Applicant/Sponsor Name: Ferring Pharmaceuticals
Submission Date: November 2, 2017
OSE RCM #: 2017-196-2
DMEPA Safety Evaluator: Matthew Barlow, RN, BSN
DMEPA Team Leader: Sarah K. Vee, PharmD

1 PURPOSE OF MEMO
DGIEP requested that we review the revised cup labeling for Clenpiq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The revised cup labeling for Clenpiq is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Barlow M. Label and Labeling Review for Clenpiq (NDA 209589). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 27. RCM No.: 2017-196-1.
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/s/

MATTHEW J BARLOW
11/06/2017

SARAH K VEE
11/06/2017
MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 27, 2017
Requesting Office or Division: Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number: NDA 209589
Product Name and Strength: Clenpiq (sodium picosulfate/magnesium oxide/anhydrous citric acid) oral solution, 10 mg/3.5 g/12 g per 160 mL
Applicant/Sponsor Name: Ferring Pharmaceuticals
Submission Date: October 25, 2017 & January 31, 2017
OSE RCM #: 2017-196-1
DMEPA Safety Evaluator: Matthew Barlow, RN, BSN
DMEPA Team Leader: Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton labeling and container label for Clenpiq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised carton labeling and container label for Clenpiq is acceptable from a medication error perspective. However, we have a recommendation for the proposed labeling for the cup to emphasize the proper use.


Reference ID: 4173375
3  RECOMMENDATIONS FOR FERRING PHARMACEUTICALS

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

A. We recommend moving the graphic, proprietary name, and established name to the bottom third of the cup to make room for both sides of the cup to include the 8-ounce marker and line along with the statement “Important: Use this cup to drink all required clear liquids after taking Clenpiq.”
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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MATTHEW J BARLOW
10/27/2017

SARAH K VEE
10/27/2017
Division of Pediatric and Maternal Health Review

Date: 10/6/2017            Date consulted: 2/13/2017

From: Catherine Roca, M.D., Medical Officer, Maternal Health
      Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
         Division of Pediatric and Maternal Health

         Lynne P. Yao, M.D., OND, Division Director
         Division of Pediatric and Maternal Health

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

Drug: CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid)

NDA: 209589

Applicant: Ferring Pharmaceuticals Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Cleansing the colon as a preparation for colonoscopy in adults

Materials Reviewed:
- Applicant’s background package for NDA 209589

Consult Question: DGIEP requests DPMH’s assistance with review of the pregnancy and lactation sections of CLENPIQ labeling.
INTRODUCTION
On 2/13/2017, the Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy and lactation sections of CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) labeling to comply with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY
On January 31, 2017, Ferring Pharmaceuticals Inc., submitted an original 505(b)(2) new drug application (NDA) for CLENPIQ, NDA 209589, based on the reference listed drug, PREPOPIK (NDA 202535). NDA 209589 is for a ready-to-drink, premixed oral solution for cleansing the colon as preparation for colonoscopy in adults.

BACKGROUND¹
Drug Characteristics
- Sodium picosulfate-
  - Is a stimulant laxative
  - Mechanism of action - hydrolyzed by colonic bacteria to form the active metabolite bis-(p-hydroxyl-phenyl)-pyridyl-2 methane (BHPM) that acts directly to stimulate peristalsis.
  - Both sodium picosulfate and BHPM had very low systemic exposure²
  - Molecular weight= 499.4 Daltons
  - The terminal half-life is 7.4 hours
- Magnesium oxide
  - Reacts with citric acid to form magnesium citrate, an osmotic agent that causes water to be retained in the gastrointestinal tract
  - Molecular weight = 40.3 Daltons
  - No protein binding
  - C_max for Magnesium levels were 20% above baseline 10 hours post administration
- Anhydrous citric acid
  - Reacts with citric acid to form magnesium citrate, an osmotic agent that causes water to be retained in the gastrointestinal tract
  - Molecular weight= 192.1 Daltons
  - Citric acid/Magnesium citrate levels were not measured

Serious adverse events from Phase 3 clinical trials include: risk of fluid and electrolyte abnormalities, arrhythmia, seizures, worsening renal function in patients with renal impairment; colonic mucosal ulcerations; and risk for aspiration in patients with impaired gag reflex.

Colonoscopy and Pregnancy
- The safety and efficacy of GI endoscopy in pregnant patients is not well studied and is only performed when there is a strong indication, and should be postponed until the second trimester when possible.³

¹ CLENPIQ proposed package insert  
² PREPOPIK (NDA 202535) Clinical Pharmacology and Biopharmaceutics Review, Dilara Japar, Ph.D., DARRTS Reference ID#3134736
• Indications for endoscopy during pregnancy include:
  o Significant or continued GI bleeding
  o Severe or refractory nausea and vomiting or abdominal pain
  o Dysphagia or odynophagia
  o Strong suspicion of colon mass
  o Severe diarrhea with negative evaluation
  o Biliary pancreatitis, symptomatic choledocholithiasis or cholangitis
  o Biliary or pancreatic ductal injury
• Risks include preterm labor, hypoxia, maternal over sedation, compression of the vena cava or aorta, and fetal demise.
• The American College of Obstetricians and Gynecologists recommend that procedures be performed in a location where obstetric and neonatal services are available, and that there be monitoring of fetal heart rate and contractions.

Current State of the Labeling
• The most recent labeling for the RLD, PREPOPIK, is in PLR, but not PLLR format.
• There is no boxed warning for embryofetotoxicity.
• Section 8.1, Pregnancy – Category B, only animal data are presented.
• Section 8.3, Nursing Mothers – No human or animal data are presented. Caution is advised when the drug is given to nursing women.
• There are no known drug-drug interactions with hormonal contraceptives, and no existing pregnancy testing/contraception recommendations.

REVIEW
PREGNANCY
Nonclinical Experience
Reproduction studies with sodium picosulfate, magnesium oxide, and anhydrous citric acid have been performed in pregnant rats following oral administration of up to 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on body surface area) during the period of organogenesis. There was no evidence of harm to the fetus due to sodium picosulfate, magnesium oxide, and anhydrous citric acid. The reproduction study in rabbits was not adequate, as treatment-related mortalities were observed at all doses. A pre and postnatal development study with sodium picosulfate, magnesium oxide, and anhydrous citric acid in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on body surface area).
Published reproduction studies with sodium picosulfate in pregnant rats and rabbits during the period of organogenesis did not show evidence of harm to the fetus at doses up to 100 mg/kg.

7 Approved PREPOPIK labeling, Drugs@FDA.gov
(approximately 49 and 98 times, respectively, the recommended human dose of 10 mg sodium picosulfate based on body surface area). For additional information, the reader is referred to the full Pharmacology/Toxicology review by Tamal Chakraborti, Ph.D.

Applicant’s Review of Literature
The applicant performed a search of the literature using Medline, Embase, BIOSIS Previews, and International Pharmaceutical Abstracts using the search terms “picosulfate sodium,” or “magnesium citrate,” or “magnesium oxide,” and “pregnancy,” “fetal development,” “pregnancy complications,” “developmental disorder,” “postnatal development,” “miscarriage or abortion,” “birth weight,” “congenital malformation,” or “embryotoxicity.”

No clinical trials or case reports of picosulfate sodium, magnesium oxide, or magnesium citrate use in pregnancy were located.

DPMH Review of Literature

Micromedex® states, “adequate and well-controlled studies of citric acid, magnesium oxide, and sodium picosulfate combination use during human pregnancy have not been conducted.”

Drugs in Pregnancy and Lactation¹⁰ does not reference PREPOPIK, sodium picosulfate, magnesium oxide, magnesium citrate, or anhydrous citric acid.

A search of the literature did not yield any clinical trials or case reports of PREPOPIK, sodium picosulfate, magnesium oxide, magnesium citrate, or anhydrous citric acid use during pregnancy.

Review of Pharmacovigilance Database
The applicant performed a search of its global safety database using the SMQs for “pregnancy and neonatal topics” from December 1980 to February, 2017. No cases related to pregnancy were found.

Summary
There are no data on PREPOPIK, sodium picosulfate, magnesium oxide, magnesium citrate, or anhydrous citric acid use in pregnant women. Data from studies in rats do not indicate a risk of adverse fetal outcomes.

LACTATION
Nonclinical Experience
There are no available animal data on sodium picosulfate or magnesium citrate in lactation.

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Review of Literature
The applicant performed a search of the literature using Medline, Embase, BIOSIS Previews, and International Pharmaceutical Abstracts and LactMed using the search terms “picosulfate sodium,” or “magnesium citrate,” or “magnesium oxide,” and “lactation,” “breastfeeding,” “breast milk,” “nursing mother,” or “human breast milk.”

The search yielded a lactation study of sodium picosulfate that is described in detail on the next page under the LactMed section.

DPMH Review of Literature
DPMH conducted a search of Medications in Mother’s Milk, the Drugs and Lactation Database (LactMed), and of the published literature in PubMed and Embase using the search terms “sodium picosulfate” or “magnesium oxide” or “anhydrous citric acid” and “lactation,” and “breast-feeding.”

Micromedex states, “Infant risk cannot be ruled out,” regarding the use of the reference drug, PREPOPIK, and breastfeeding.

Sodium picosulfate, magnesium oxide, magnesium citrate, anhydrous citric acid, and PREPOPIK are not referenced in Drugs in Pregnancy and Lactation or Medications and Mother’s milk.

Sodium picosulfate
Sodium picosulfate is referenced in LactMed, and the following is noted under Summary of Use during Lactation:

“Sodium picosulfate is not absorbed from the gastrointestinal tract, and its active metabolite, which is absorbed, is not detectable in breastmilk. Sodium picosulfate can be taken during breastfeeding and no special precautions are required.”

In addition, LactMed notes the following regarding sodium picosulfate drug levels in breastmilk:

“Maternal Levels. Sixteen postpartum women who were not breastfeeding, but were producing at least 200 mL of milk daily by breast pump were given either oral enteric-coated bisacodyl tablets (Dulcolax) 10 mg daily or oral liquid sodium picosulfate (Laxoberal) 10 mg daily for 7 days. Both drugs are prodrugs metabolized to the active

13 http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
drug, bis-(p-hydroxyphenyl)-2-pyridyl-2-methane (BHPM). All breastmilk was collected daily from the day before drug administration to 2 days after the last dose. Free and conjugated BHPM were undetectable (<1 mcg/L) in all milk samples."^{17}

No information related to the effects on the breastfed infant or milk production were found.

**Magnesium Oxide**
Magnesium Oxide is also referenced in LactMed,^{13} and the following is noted under Summary of Use during Lactation:

“No information is available on the clinical use of magnesium oxide during breastfeeding. However, other magnesium salts have been studied. A study on the use of magnesium hydroxide during breastfeeding found no adverse reactions in breastfed infants. Intravenous magnesium increases milk magnesium concentrations only slightly. Oral absorption of magnesium by the [breastfed] infant is poor, so maternal magnesium hydroxide is not expected to affect the breastfed infant's serum magnesium. Magnesium oxide supplementation during pregnancy might delay the onset of lactation, but it can be taken during breastfeeding and no special precautions are required.”

**Reviewer comment:**
Regarding the phrase noted above “Oral absorption of magnesium by the infant is poor," in a nursing mother who is taking magnesium, the absorption of magnesium by the breastfed infant is expected to be low. Therefore, it is unlikely that a significant amount of magnesium will be ingested by the breast fed infant to affect the infant’s serum magnesium.

LactMed^{13} notes the following regarding Magnesium levels in breast milk:

“Maternal Levels. Ten women with pre-eclampsia were given 4 grams of magnesium sulfate intravenously followed by 1 gram per hour until 24 hours after delivery. While the average serum magnesium was 35.5 mg/L in treated women compared to 18.2 mg/L in 5 untreated controls, colostrum magnesium levels at the time of discontinuation of the infusion was 64 mg/L in treated women and 48 mg/L in the controls. By 48 hours after discontinuation, colostrum magnesium levels were only slightly above control values and by 72 hours they were virtually identical to controls.”^{18}

**Reviewer comment:**
The current recommended dietary allowance for magnesium in infants from birth to six months of age is 30mg per day and in infants from 7-12 months is 75mg per day.^{19}

In a study on magnesium balance in preterm and term infants( ages 2.6 to 4.7 weeks), the data were presented using mg/L. Infant formula contained 50.2 - 96 mg/L of magnesium and the

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range of magnesium in human milk ranged from 21.2-44 mg/L. In a term infant that is formula-fed, the magnesium retention is 41.3% versus 66.5% in a breastfed infant.\textsuperscript{20}

LacMed\textsuperscript{13} notes the following regarding the effects of magnesium (taken by a nursing mother) on breastfed infants:

“Fifty mothers who were in the first day postpartum received 15 mL of either mineral oil or an emulsion of mineral oil and another magnesium salt, magnesium hydroxide equivalent to 900 mg of magnesium hydroxide, although the exact number who received each product was not stated. Additional doses were given on subsequent days if needed. None of the breastfed infants was noted to have any markedly abnormal stools, but all of the infants also received supplemental feedings.”\textsuperscript{21}

\textbf{Reviewer comment:}
\textit{Regarding the phrase “markedly abnormal stools,” the original reference\textsuperscript{20} notes that “all infant stools in both groups were within normal range of consistency.”}

LactMed\textsuperscript{13} notes the following regarding the effects of magnesium on lactation and breastmilk:

“One mother who received intravenous magnesium sulfate for 3 days for pregnancy-induced hypertension had lactogenesis delayed until day 10 postpartum. No other specific cause was found for the delay, although a complete work-up was not done.\textsuperscript{22} A subsequent controlled clinical trial found no evidence of delayed lactation in mothers who received intravenous magnesium sulfate therapy.\textsuperscript{23} Some, but not all, studies have found a trend toward increased time to the first feeding or decreased sucking in infants of mothers treated with intravenous magnesium sulfate during labor because of placental transfer of magnesium to the fetus.\textsuperscript{24,25}

A study in 40 pairs of matched healthy women with vaginally delivered singleton pregnancies, outcome endpoints were compared in those receiving continuous oral magnesium aspartate HCl supplementation mean dose of 459 mg daily (range 365 to 729 mg of magnesium daily) for at least 4 weeks before delivery versus non-supplemented controls. In the magnesium group, significantly fewer women could breastfeed their infants exclusively at discharge (63\% vs 80\%).\textsuperscript{26}

\textbf{Reviewer comment:}
\textit{DPMH discussed the oral bioavailability of magnesium oxide, compared to the other magnesium salts (magnesium hydroxide and magnesium sulfate) described above, with the Clinical}

\textsuperscript{21} Baldwin WF. Clinical study of senna administration to nursing mothers: assessment of effects on infant bowel habits. Can Med Assoc J. 1963;89:566-7
Pharmacology Team via e-mail on 10/4/2017. The Clinical Pharmacology Team noted that there is no good information on the oral bioavailability of magnesium oxide or magnesium citrate. Since the action of magnesium oxide and magnesium citrate is local, absorption would not be significant. The Clinical Pharmacology team noted that it would be sufficient to note that information on the presence of magnesium oxide in breast milk is not available in subsection 8.2 of CLENPIQ labeling.

A search of the published literature did not yield any additional references.

Review of Pharmacovigilance Database
The applicant performed a search of its global safety database using the SMQs for “neonatal topics” from December 1980 to February 2017. No cases related to breastfeeding were found.

Summary
No data are available on the effects of the combined effects of sodium picosulfate, magnesium oxide, and anhydrous citric acid on the breastfed infant or lactation. In a lactation study of 16 women, sodium picosulfate and its active metabolite BHPM were not detected in human milk. There are no data specific to magnesium oxide or magnesium citrate in lactation, but data on intravenous magnesium sulfate indicate that magnesium sulfate increases milk magnesium concentrations only slightly. In a study examining the effects of laxatives (including a magnesium hydroxide containing preparation) taken by breastfeeding mothers, there was no increase in the number and consistency of stools in infants exposed to laxatives via breastfeeding. Some data from magnesium supplementation during pregnancy suggest that magnesium might delay the onset of lactation; however, most of these studies were either of intravenous magnesium preparations or of multiple oral doses. It is not clear how this data relates to use of a single dose oral preparation.

DPMH recommends the following risk/benefit statement in subsection 8.2, Lactation:

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CLENPIQ and any potential adverse effects on the breastfed infant from CLENPIQ or from the underlying maternal condition.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
In an oral fertility study in rats, sodium picosulfate, magnesium oxide, and anhydrous citric acid did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on body surface area). For additional information, the reader is referred to the full Pharmacology/Toxicology review by Tamal Chakraborti, Ph.D.

Applicant’s Review of Literature
The applicant performed a search of the literature using Medline, Embase, BIOSIS Previews, and International Pharmaceutical Abstracts using the search terms “picosulfate sodium,” or “magnesium citrate,” or “magnesium oxide,” or “anhydrous citric acid,” and “fertility,” or “infertility.”

A search of the published literature did not yield any references.

DPMH Review of Literature
DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, terms “picosulfate sodium,” or “magnesium citrate,” or “magnesium oxide,” and “contraception,” “oral contraceptives,” “fertility,” or “infertility.”

A search of the published literature did not yield any clinical trials or case reports related to either fertility or hormonal contraception.

Review of Pharmacovigilance Database
The applicant performed a search of its global safety database using the SMQs for “fertility disorders” from December 1980 to February 2017. One case of a 42-year-old woman being treated for chronic constipation with PICOLAX was found in 2004. The patient reported unusual menstrual bleeding following 9 months treatment with PICOLAX and 28 days of treatment with norethisterone. No serious adverse events were associated with this case.

Summary
There are no published reports related to picosulfate sodium, magnesium citrate, magnesium oxide, or anhydrous citric acid related to human infertility or hormonal contraceptive use. There was one case report from the pharmacovigilance database related to menstrual bleeding with concomitant use of a progestin. Animal data do not show an adverse effect of sodium picosulfate, magnesium oxide, and anhydrous citric acid on male or female fertility. Therefore, DPMH recommends that section 8.3 be omitted from the labeling.

CONCLUSIONS
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of CLENPIQ labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” sections.

- **Lactation, Section 8.2**
  - The “Lactation” subsection of labeling was formatted in the PLLR format to include: the “Risk Summary.”

LABELING RECOMMENDATIONS
DPMH revised sections 8.1, and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for approved labeling for the reference drug, PREPOPIK.)
DPMH Proposed Pregnancy and Lactation Labeling for CLENPIQ

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no data with CLENPIQ use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats when sodium picosulfate and magnesium oxide, and anhydrous citric acid were administered orally at doses 1.2 times the recommended human dose based on body surface area during the period of organogenesis.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
Reproduction studies with sodium picosulfate, magnesium oxide, and anhydrous citric acid have been performed in pregnant rats following oral administration of up to 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on body surface area) during the period of organogenesis. There was no evidence of harm to the fetus due to sodium picosulfate, magnesium oxide, and anhydrous citric acid. The reproduction study in rabbits was not adequate, as treatment-related mortalities were observed at all doses. A pre and postnatal development study with sodium picosulfate, magnesium oxide, and anhydrous citric acid in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on body surface area).

Published reproduction studies with sodium picosulfate in pregnant rats and rabbits during the period of organogenesis did not show evidence of harm to the fetus at doses up to 100 mg/kg (approximately 49 and 98 times, respectively, the recommended human dose of 10 mg sodium picosulfate based on body surface area).

8.2 Lactation
Risk Summary
There are no data on the presence of magnesium oxide or anhydrous citric acid in either human or animal milk, the effects on the breastfed infant or the effects on milk production. Published data on lactating women indicate that the active metabolite of sodium picosulfate, bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) remained below the limit of detection (1 ng/mL) in breast milk after both single and multiple doses of 10 mg/day. There are no data on the effects of sodium picosulfate on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CLENPIQ and any potential adverse effects on the breastfed infant from CLENPIQ or from the underlying maternal condition.
APPENDIX A – Approved Labeling from the Reference Drug PREPOPIK

HIGHLIGHTS OF PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY
Pregnancy Category B
Reproduction studies with PREPOPIK have been performed in pregnant rats at oral doses up to 2000 mg/kg/day (about 1.2 times the recommended human dose based on the body surface area), and did not reveal any evidence of impaired fertility or harm to the fetus due to PREPOPIK. The reproduction study in rabbits was not adequate, as treatment-related mortalities were observed at all doses. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on the body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PREPOPIK should be used during pregnancy only if clearly needed.

8.3 NURSING MOTHERS
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PREPOPIK is administered to a nursing woman.
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/s/

CATHERINE A ROCA
10/06/2017

MIRIAM C DINATALE
10/06/2017

LYNNE P YAO
10/12/2017
PATIENT LABELING REVIEW

Date: September 29, 2017

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Error Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid)

Dosage Form and Route: oral solution

Application Type/Number: 209589

Applicant: Ferring Pharmaceuticals
1 INTRODUCTION

On January 31, 2017, Ferring Pharmaceuticals submitted for the Agency’s review a new drug application for CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution intended for cleansing of the colon as a preparation for colonoscopy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on February 15, 2017 and February 14, 2017 respectively for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) and Instructions for Use (IFU) for CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution.

2 MATERIAL REVIEWED

- Draft CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) MG and IFU received on February 15, 2017, and received by DMPP and OPDP on September 25, 2017.
- Draft CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) Prescribing Information (PI) received on February 15, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 2017.

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 and 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 reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

Reference ID: 4160961
• ensured that the MG and IFU meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
• ensured that the MG and IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS
The MG and IFU is acceptable with our recommended changes.

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

Please let us know if you have any questions.
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/s/

AMANPREET K SARAI
09/29/2017

MARcia B WILLIAMS
09/29/2017

MEETA N Patel
09/29/2017

LASHAWN M GRIFFITHS
09/29/2017
**Memorandum**

**Date:** September 29, 2017  
**To:** Maureen Dewey, MPH, Regulatory Project Manager, (DGIEP)  
**From:** Meeta Patel, Pharm.D., Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)  
**CC:** Kathleen Klemm, Team Leader, OPDP  
**Subject:** OPDP Labeling Comments for CLENPIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution  
**NDA:** 209589

In response to DGIEP consult request dated February 14, 2017, OPDP has reviewed the proposed product labeling (PI), medication guide (MG), and instructions for use (IFU) for the original NDA submission for Clenpiq.

OPDP’s comments on the proposed labeling are based on the draft PI and MG received by electronic mail from DGIEP on September 26, 2017. We have no comments on the proposed PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed MG and IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEETA N PATEL
09/29/2017

Reference ID: 4160637
LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

**Date of This Review:** September 20, 2017
**Requesting Office or Division:** Division of Gastroenterology & Inborn Error Products (DGIEP)
**Application Type and Number:** NDA 209589
**Product Name and Strength:** Clenpiq (sodium picosulfate/magnesium oxide/anhydrous citric acid) oral solution, 10 mg/3.5 g/12 g per 160 mL
**Product Type:** Multi-Ingredient Product
**Rx or OTC:** Rx
**Applicant/Sponsor Name:** Ferring Pharmaceuticals
**Submission Date:** January 31, 2017
**OSE RCM #:** 2017-196
**DMEPA Safety Evaluator:** Matthew Barlow, RN, BSN
**DMEPA Team Leader:** Sarah K. Vee, PharmD
1 REASON FOR REVIEW
This review is in response to DGIEP’s request for DMEPA to evaluate the proposed carton label, container labeling, and Prescribing Information (PI) submitted by the applicant under NDA 209589. The proposed labels and labeling were submitted on January 31, 2017.

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

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
The Applicant submitted the proposed labels and labeling under the NDA 209589 on January 31, 2017. This application was submitted as a 505(b)(2), referencing the listed drug Prepopik, NDA 202535. We performed a risk assessment of the submitted labels and labeling for areas of vulnerability that may lead to medication errors. We note the proposed carton labeling and container labels can be revised to increase clarity and understanding of important information. We note the established name does not have commensurate prominence with the proprietary name, which can be revised to align with current display standards and make it more legible. Additionally, we note the display of the strength is difficult to read as it is currently displayed, which can be modified to improve legibility and clarity. Also, we note there is no ‘usual dose’ statement, lot number, or expiration date, which can be added to align with current labeling standards. Furthermore, we note the proposed container label lacks a barcode, therefore we recommend adding a barcode to the container label to fall in line with current standards. We provide recommendations in section 4.1 below.

4 CONCLUSION & RECOMMENDATIONS
We note areas of the proposed labels and labeling that can be revised to improve the prominence and clarity of important information.
4.1 RECOMMENDATIONS FOR FERRING PHARMACEUTICALS

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

A. Carton and Container Labeling
   a. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Additionally, the established name is not at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with 21 CFR 201.10(g)(2).
   b. Revise the strength presentation to improve legibility and prominence to align with current labeling regulations per 21 CFR 201.15(a)(6). This will increase emphasis of this important information. Additionally revise the strength statement to read as follows “10 mg/3.5 g/12 g per 160 mL bottle.”
   c. Add a “Usual Dose” statement to the labeling (e.g. side panel) per 21 CFR 201.55.
   d. Add the Lot Number and Expiration date on the carton and container labeling as required per 21 CFR 201.10(i)(1) and 21 CFR 201.17.
   e. We recommend placing the storage information on the side panel of the carton and container labeling to minimize clutter on the Principal Display Panel (PDP).

B. Container Labeling
   a. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to the carton and container labeling as required per 21 CFR 201.25(c)(2). The barcode should be surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i). The barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g. perforation).
## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Clenpiq that Ferring Pharmaceuticals submitted on January 31, 2017, and the listed drug (LD).

| **Table 2. Relevant Product Information for Clenpiq and the Listed Drug** |
|---------------------------|---------------------------|---------------------------|
| **Product Name**          | Clenpiq                   | Prepopik                  |
| **Initial Approval Date** | N/A                       | 7/16/2012                 |
| **Active Ingredient**     | Sodium picosulfate/magnesium oxide/anhydrous citric acid | |
| **Indication**            | Cleansing of the colon as a preparation for colonoscopy in adults | |
| **Route of Administration** | Oral                     | For Oral Solution         |
| **Dosage Form**           | Oral Solution             | For Oral Solution         |
| **Strength**              | •10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid per 160 mL | •Each of 2 packets contains 16.1 g of powder: 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid |
| **Dose and Frequency**    | **Split-Dose Dosage Regimen (Preferred Method)** | **Split-Dose Dosing Regimen (Preferred Method)** |
|                           | The Split-Dose regimen is the preferred dosing method. Instruct patients to take two separate doses in conjunction with fluids, as follows: Dose 1 – On the day before colonoscopy: •Instruct patients to consume only clear liquids (no solid food or dairy) on the day before the colonoscopy up until 2 hours before the time of the colonoscopy. •Take the first dose (1 bottle) of CLENPIQ during the evening before the colonoscopy (e.g., 5:00 to 9:00 PM). •Follow CLENPIQ by drinking | The Split-Dose regimen is the preferred dosing method. Instruct patients to take two separate doses in conjunction with fluids, as follows: -Take the first dose during the evening before the colonoscopy (e.g., 5:00 to 9:00 PM) followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before bed. Consume clear liquids within 5 hours. -Take second dose, the next day approximately 5 hours before the |
five 8 ounce cups (cup provided) of clear liquids (40 ounces total) within 5 hours and before bed.

Dose 2 – Next morning on the day of colonoscopy (start approximately 5 hours prior to colonoscopy):
• Continue to consume only clear liquids (no solid food or dairy).
• Take the second dose (the second bottle) of CLENPIQ.
• Following the CLENPIQ dose, drink at least three 8 ounce cups (cup provided) of clear liquids (24 ounces) at least 2 hours before the colonoscopy.

Day-Before Dosage Regimen (Alternative Method)
The Day-Before regimen is the alternative dosing method for patients for whom the Split-Dosing is inappropriate.
Instruct patients to take two separate doses in conjunction with fluids, as follows:
Dose 1 – On the day before colonoscopy:
• Instruct patients to consume only clear liquids (no solid food or dairy) on the day before the colonoscopy up until 2 hours before the time of the colonoscopy.
• Take the first dose (1 bottle) of CLENPIQ in the afternoon or early evening before the colonoscopy (e.g., 4:00 to 6:00 PM).

colonoscopy followed by at least three 8-ounce drinks of clear liquids before the colonoscopy. Consume clear liquids within 5 hours up until 2 hour before the time of the colonoscopy.

Day-Before Dosing Regimen (Alternative Method)
The Day-Before regimen is the alternative dosing method for patients for whom the Split-Dosing is inappropriate. Instruct patients to take two separate doses in conjunction with fluids, as follows:
• Take the first dose in the afternoon or early evening (e.g., 4:00 to 6:00 PM) before the colonoscopy followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before the next dose. Consume clear liquids within 5 hours.
• Take the second dose approximately 6 hours later in the late evening (e.g., 10:00 PM to 12:00 AM), the night before the colonoscopy followed by three 8-ounce drinks of clear liquids before bed. Consume clear liquids within 5 hours.
• Following the CLENPIQ dose, drink five 8 ounce cups (cup provided) of clear liquids (40 ounces total) within 5 hours and before the next dose.

Dose 2 – Approximately 6 hours later in the evening the night before the colonoscopy (e.g., 10:00 PM to 12:00 AM):
• Take the second dose (the second bottle) of CLENPIQ.
• Following the CLENPIQ dose, drink three 8 ounce cups (cup provided) (24 ounces) of clear liquids within 5 hours and before bed.

**How Supplied**

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>How Supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>supplied in a carton containing two bottles, each holding 5.4 ounces of cranberry-flavored, colorless to slightly yellow, clear oral solution, along with an eight-ounce cup for measuring fluids for hydration. Each bottle contains 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid.</td>
<td>Supplied in a carton containing 2 packets, each holding 16.1 grams of powder for oral solution, along with a pre-marked dosing cup. Each packet contains 10 mg sodium picosulfate, 3.5 g magnesium oxide and 12 g anhydrous citric acid.</td>
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</tbody>
</table>

**Storage**

<table>
<thead>
<tr>
<th>Storage</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store at 25°C (77°F). Excursions permitted at 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Do not refrigerate or freeze.</td>
<td>Store at 25°C (77°F). Excursions permitted at 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].</td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 15, 2017, we searched DMEPA’s previous reviews using the terms, Clenpiq. Our search identified no previous relevant reviews.

APPENDIX C. HUMAN FACTORS STUDY—N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 15, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

<table>
<thead>
<tr>
<th>ISMP Newsletters Search Strategy</th>
</tr>
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<tbody>
<tr>
<td><strong>ISMP Newsletter(s)</strong></td>
</tr>
<tr>
<td><strong>Search Strategy and Terms</strong></td>
</tr>
</tbody>
</table>

D.2 Results

The search criteria outlined above yielded no cases.
APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods
On March 15, 2017, we searched FAERS using the criteria in the table below and identified twelve cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter. We excluded eleven cases because they described issues that not applicable to this review, and we excluded one case because it did not include enough information or a definitive root cause.

<table>
<thead>
<tr>
<th>Criteria Used to Search FAERS</th>
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<tbody>
<tr>
<td>Initial FDA Receive Dates:</td>
</tr>
<tr>
<td>January 31, 2014 to March 1, 2017</td>
</tr>
<tr>
<td>Product Name:</td>
</tr>
<tr>
<td>Prepopik</td>
</tr>
<tr>
<td>Event:</td>
</tr>
<tr>
<td>SMQ Medication errors (Narrow)</td>
</tr>
<tr>
<td>Country (Derived):</td>
</tr>
<tr>
<td>USA</td>
</tr>
</tbody>
</table>

E.2 Results
Our search identified twelve cases, of which eleven described errors not relevant to this review. One case did not include enough information or a definitive root cause, and we note the IFU contains a clear statement that the patient can drink clear liquids until 2 hours before the procedure.

E.3 List of FAERS Case Numbers
Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

E.4 Description of FAERS
The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA’s postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA’s Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:


APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Clenpiq labels and labeling submitted by Ferring Pharmaceuticals on January 31, 2017.

- Container label
- Carton labeling
- Cup label
- Instructions for Use (not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

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

/s/

MATTHEW J BARLOW
09/20/2017

SARAH K VEE
09/20/2017
Pharmacovigilance Memorandum

Date: April 20, 2017

Reviewer(s): Lisa Harinstein, PharmD, Safety Evaluator
Division of Pharmacovigilance (DPV-I)

Team Leader(s): Eileen Wu, PharmD, Team Leader
DPV-I

Deputy Director: Monica Muñoz, PharmD, MS, BCPS
DPV-I

Product Name(s): Prepopik (sodium picosulfate/ magnesium oxide/ anhydrous citric acid)

Subject: All reported adverse events, including hyponatremia, seizures, ischemic colitis, electrolyte imbalance, and ulcerative colitis flare

Application Type/Number: NDA 202535, NDA 209589

Applicant/Sponsor: Ferring Pharmaceuticals

OSE RCM #: 2017-377
1 INTRODUCTION

This review evaluated the FDA Adverse Event Reporting System (FAERS) database for all adverse event reports, including five adverse events of special interest (AESIs), with Prepopik powder for oral solution (sodium picosulfate/ magnesium oxide/ anhydrous citric acid, NDA 202535) during the February 1, 2014 to February 28, 2017 time interval to inform the Division of Gastroenterology and Inborn Errors Products (DGIEP) as they review a 505(b)(2) NDA 209589 application for Clenpiq oral solution (sodium picosulfate/ magnesium oxide/ anhydrous citric acid). This review refers to the five following adverse events as AESIs: 1) hyponatremia, 2) electrolyte imbalance, 3) seizures/convulsions, 4) ischemic colitis, and 5) ulcerative colitis flare.

1.1 BACKGROUND

On January 31, 2017, Ferring Pharmaceuticals submitted a 505(b)(2) NDA 209589 application for Clenpiq oral solution (sodium picosulfate/ magnesium oxide/ anhydrous citric acid). The 505(b)(2) relies on the safety and efficacy findings of the reference listed drug (RLD), NDA 202535 Prepopik powder for oral solution (sodium picosulfate/ magnesium oxide/ anhydrous citric acid), also manufactured by Ferring Pharmaceuticals. The proposed product contains the same active ingredient as the RLD (sodium picosulfate/ magnesium oxide/ anhydrous citric acid), but is formulated as a ready-to-drink, pre-mixed oral solution instead of a powder for oral solution. The proposed indication is identical to the RLD product – indicated for cleansing of the colon as a preparation for colonoscopy in adults.

On February 21, 2017, DGIEP requested that DPV-I search the FAERS database for postmarketing reports of all adverse events in all age groups, including the five AESIs associated with Prepopik since February 1, 2014 (see Section 1.2 for more information about choice of initial search date and adverse event terms).1

1.2 PRIOR DPV-I SAFETY REVIEWS

Prior to submission of Prepopik NDA 202535, the combination product of sodium picosulfate/ magnesium oxide/ citric acid was approved for use as a bowel preparation in foreign countries under the tradenames PicoPrep, Picolax, Pico-Salax, and Citrafleet. A citizen petition was submitted on September 29, 2011 requesting FDA to refrain from approval or at least require that the label for the approved product include a boxed warning for the risk of electrolyte imbalances and ischemic colitis.2 The petitioner alleged the following risks related to the use of sodium picosulfate and magnesium citrate (magnesium oxide and citric acid react to form magnesium citrate in solution) or sodium picosulfate alone as part of the basis for their request:

1) When use for bowel preparation, sodium picosulfate, magnesium oxide, and citric acid fails to correct electrolyte imbalances such as hyponatremia and hypokalemia resulting in dehydration, convulsion, syncope, unconsciousness, and metabolic acidosis.

---

1 The data lock date of the completed FAERS search for the FDAAA Section 915 NME Postmarket Safety Summary Analysis was January 31, 2014.

Reference ID: 4087114
2) The higher 20 mg dosage of sodium picosulfate is associated with mucosal inflammation and ulceration, thus increases the risks of ischemic colitis and flare of ulcerative colitis.

On March 29, 2012, DGIEP requested DPV-I to review cases of ischemic colitis, electrolyte imbalance, and flare of ulcerative colitis possibly related to sodium picosulfate/ magnesium oxide/ citric acid contained in the Adverse Event Reporting System (AERS) database to assist with DGIEP’s response to the citizen petition for NDA 202535. Search of the AERS database identified a single foreign case of ischemic colitis, three foreign cases of electrolyte imbalances, and no cases of flare of ulcerative colitis associated with the use of sodium picosulfate/ magnesium oxide/ citric acid. Because of the small number of cases and limitations related to AERS reports, DPV-I was unable to assess the safety of sodium picosulfate/ magnesium oxide/ citric acid; the data contained in the DPV-I review should be considered supportive to findings from reviews of clinical trial data, Periodic Safety Update Reports from foreign countries where the product is marketed, and the medical literature.

On July 16, 2012, FDA approved NDA 202535 Prepopik powder for oral solution (sodium picosulfate/ magnesium oxide/ citric acid) and responded to the citizen petition. FDA denied the citizen petition request of 1) refraining from approving any NDA containing the active ingredients of sodium picosulfate 10 mg/ magnesium oxide 3.5 g/ citric acid 12 g for bowel cleansing and, 2) if approval of any NDA for such a formulation, require labeling to carry a boxed warning describing the heightened risks of electrolyte imbalance and ischemic colitis. The approved product labeling for Prepopik includes risk of fluid and electrolyte abnormalities, arrhythmias, seizures, renal impairment, colonic mucosal ulceration, ischemic colitis, and ulcerative colitis in the Warnings and Precautions section.

On June 16, 2014, DPV-I completed the FAERS overview section of a FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis of all serious and non-serious adverse events reported with Prepopik (sodium picosulfate/ magnesium oxide/ citric acid) between July 16, 2012 (date of U.S. approval) and January 31, 2014. The intent of the analysis was to: 1) identify a potential increase in frequency or severity of labeled adverse events, 2) identify any new unlabeled adverse events, and 3) evaluate adverse events that are considered rare or serious with Prepopik. The FAERS search strategy yielded 160 reports. A high-level review of the reports was completed. The analysis noted the following labeled events: hyponatremia and convulsions. There were 12 cases of hyponatremia; all reported a serious outcome including one death. There were 12 cases of convulsions and three cases of grand mal convulsions; all reported a serious outcome including two deaths. Because all identified reports of hyponatremia and convulsions/ grand mal convulsions had a serious outcome, DPV-I recommended close monitoring of the two adverse events.

b The denial asserted that the risk for complications associated with electrolyte imbalance can be minimized by, 1) selecting the most appropriate bowel cleansing agent for each patient, 2) highlighting important of adherence to preparation instructions, and 3) employing increased electrolyte monitoring in patients who are considered “at risk” (such as older patients, patients receiving diuretics, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs)). There was insufficient evidence to conclude the product was associated with an increased risk of ischemic colitis.
1.3 SELECTED PRODUCT LABELING FOR PREPOPIK

The five AESIs are labeled within Warnings and Precautions Section 5 of the Prepopik product label— hyponatremia and electrolyte imbalance (Section 5.1), seizures (Section 5.2), and ischemic colitis and ulcerative colitis flare (Section 5.5). The current U.S. label for Prepopik reads as follows:4

-----------------------5 WARNINGS AND PRECAUTIONS------------------------

5.1 Serious Fluid and Serum Chemistry Abnormalities
Advis[e patients to hydrate adequately before, during, and after the use of Prepopik®. Use caution in patients with congestive heart failure when replacing fluids. If a patient develops significant vomiting or signs of dehydration including signs of orthostatic hypotension after taking Prepopik®, consider performing post-colonoscopy lab tests (electrolytes, creatinine, and BUN) and treat accordingly. Approximately 20% of patients in both arms (Prepopik®, 2L of PEG + E plus two x 5-mg bisacodyl tablets) of clinical trials of Prepopik® had orthostatic changes (changes in blood pressure and/or heart rate) on the day of colonoscopy. In clinical trials orthostatic changes were documented out to seven days post colonoscopy. [see Adverse Reactions (6.1, 6.2)]

Fluid and electrolyte disturbances can lead to serious adverse events including cardiac arrhythmias or seizures and renal impairment. Fluid and electrolyte abnormalities should be corrected before treatment with Prepopik®. In addition, use caution when prescribing Prepopik® for patients who have conditions or who are using medications that increase the risk for fluid and electrolyte disturbances or that may increase the risk of adverse events of seizure, arrhythmia, and renal impairment.

5.2 Seizures
There have been reports of generalized tonic-clonic seizures with the use of bowel preparation products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia) and low serum osmolality. The neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities. Use caution when prescribing Prepopik® for patients with a history of seizures and in patients at risk of seizure, such as patients taking medications that lower the seizure threshold (e.g., tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, patients with known or suspected hyponatremia. [see Adverse Reactions (6.2)]

5.3 Use in Patients with Renal Impairment
As in other magnesium containing bowel preparations, use caution when prescribing Prepopik® for patients with impaired renal function or patients taking concomitant medications that may affect renal function (such as diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or non-steroidal anti-inflammatory drugs). These patients may be at increased risk for renal injury. Advise these patients of the importance of adequate hydration before, during and after the use of Prepopik®. Consider performing baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in these patients. In patients with severely reduced renal function (creatinine clearance < 30 mL/min), accumulation of magnesium in plasma may occur.

5.4 Cardiac Arrhythmias
There have been rare reports of serious arrhythmias associated with the use of ionic osmotic laxative products for bowel preparation. Use caution when prescribing Prepopik® for patients at increased risk of arrhythmias (e.g., patients with a history of prolonged QT, uncontrolled arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy). Pre-dose and post-colonoscopy ECGs should be considered in patients at increased risk of serious cardiac arrhythmias.

5.5 Colonic Mucosal Ulceration, Ischemic Colitis and Ulcerative Colitis
Osmotic laxatives may produce colonic mucosal aphthous ulcerations and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Concurrent use of additional stimulant laxatives
with Prepopik® may increase this risk. The potential for mucosal ulcerations should be considered when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease. [see Adverse Reactions (6.2)]

5.6 Use in Patients with Significant Gastrointestinal Disease
If gastrointestinal obstruction or perforation is suspected, perform appropriate diagnostic studies to rule out these conditions before administering Prepopik®. Use with caution in patients with severe active ulcerative colitis.

5.7 Aspiration
Patients with impaired gag reflex and patients prone to regurgitation or aspiration should be observed during the administration of Prepopik®. Use with caution in these patients.

5.8 Not for Direct Ingestion
Each packet must be dissolved in 5 ounces of cold water and administered at separate times according to the dosing regimen. Ingestion of additional water is important to patient tolerance. Direct ingestion of the undissolved powder may increase the risk of nausea, vomiting, dehydration, and electrolyte disturbances.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
In randomized, multicenter, controlled clinical trials, nausea, headache, and vomiting were the most common adverse reactions (>1%) following Prepopik® administration. The patients were not blinded to the study drug. Since abdominal bloating, distension, pain/cramping, and watery diarrhea are known to occur in response to colon cleansing preparations, these effects were documented as adverse events in the clinical trials only if they required medical intervention (such as a change in study drug or led to study discontinuation, therapeutic or diagnostic procedures, met the criteria for a serious adverse event), or showed clinically significant worsening during the study that was not in the frame of the usual clinical course, as determined by the investigator.

Electrolyte Abnormalities
In general, Prepopik® was associated with numerically higher rates of abnormal electrolyte shifts on the day of colonoscopy compared to the preparation containing 2L of PEG + E plus two x 5-mg bisacodyl tablets (Table 2). These shifts were transient in nature and numerically similar between treatment arms at the Day 30 visit.

6.2 Postmarketing Experience

Allergic reactions
Cases of hypersensitivity reactions including rash, urticaria, and purpura have been reported.

Electrolyte abnormalities
There have been reports of hypokalemia, hyponatremia and hypermagnesemia with the use of Prepopik® for colon preparation prior to colonoscopy.

Gastrointestinal:
Abdominal pain, diarrhea, fecal incontinence, and proctalgia have been reported with the use of Prepopik® for colon preparation prior to colonoscopy. There have been isolated reports of reversible aphthoid ileal ulcers. Ischemic colitis has been reported with the use of Prepopik® for colon preparation prior to colonoscopy. However, a causal relationship between these ischemic colitis cases and the use of Prepopik® has not been established.

Neurologic,
There have been reports of generalized tonic-clonic seizures associated with and without hyponatremia in epileptic patients.
2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched FAERS with the strategy described in Table 1.

<table>
<thead>
<tr>
<th>Table 1. FAERS Search Strategy*</th>
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<tbody>
<tr>
<td><strong>Date of Search</strong></td>
</tr>
<tr>
<td><strong>Time Period of Search</strong></td>
</tr>
<tr>
<td><strong>Search Type</strong></td>
</tr>
<tr>
<td><strong>Product Terms</strong></td>
</tr>
</tbody>
</table>

* See Appendix A for a description of the FAERS database.
† The data lock date of the previous FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis was January 31, 2014.

3 RESULTS/DATA

The FAERS search on March 1, 2017 yielded 473 reports. Table 2 contains the descriptive characteristics of the 473 adverse event reports with sodium picosulfate/ magnesium oxide/ citric acid. Table 3 lists the most frequently reported MedDRA Preferred Terms (PTs) for FAERS reports with serious and non-serious outcomes. Table 4 lists the most frequently reported MedDRA PTs for FAERS reports with serious outcomes. PTs that refer to AESIs are bolded in table 3 and 4.

<table>
<thead>
<tr>
<th>Table 2. Descriptive Characteristics of FAERS Reports for sodium picosulfate/ magnesium oxide/ citric acid, Received by FDA from February 1, 2014 to February 28, 2017 (N=473)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
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<td><strong>Report type</strong></td>
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<tr>
<td><strong>Serious Outcomes^ (n=165)</strong></td>
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</table>

* May include duplicates.
^ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.
Table 3. Most Frequently Reported MedDRA PTs with N ≥ 10 for sodium picosulfate/ magnesium oxide/ citric acid, Received by FDA from February 1, 2014 to February 28, 2017, Sorted by Decreasing Number of FAERS Reports per PT

<table>
<thead>
<tr>
<th>Row</th>
<th>MedDRA PT</th>
<th>Number of FAERS Reports*</th>
<th>Labeled (Yes/No), Location or Other Category†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug ineffective</td>
<td>157</td>
<td>No; U</td>
</tr>
<tr>
<td>2</td>
<td>Vomiting</td>
<td>85</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Not for Direct Ingestion (5.8)), AR, PCI, MG</td>
</tr>
<tr>
<td>3</td>
<td>Nausea</td>
<td>68</td>
<td>Yes; W/P (Not for Direct Ingestion (5.8)), AR, PCI, MG</td>
</tr>
<tr>
<td>4</td>
<td>Diarrhoea</td>
<td>57</td>
<td>Yes; IR, AR, MG</td>
</tr>
<tr>
<td>5</td>
<td>Headache</td>
<td>46</td>
<td>Yes; AR, MG</td>
</tr>
<tr>
<td>6</td>
<td><strong>Hyponatraemia</strong></td>
<td>38</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Seizure (5.2)), AR, DI</td>
</tr>
<tr>
<td>7</td>
<td>Dizziness</td>
<td>36</td>
<td>Yes; MG</td>
</tr>
<tr>
<td>8</td>
<td>Loss of consciousness</td>
<td>28</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>9</td>
<td>Abdominal pain</td>
<td>27</td>
<td>Yes; AR, PCI, MG</td>
</tr>
<tr>
<td>10</td>
<td>Malaise</td>
<td>24</td>
<td>No; co-reported with other adverse events already labeled such as headache, diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td>11</td>
<td>Treatment noncompliance</td>
<td>20</td>
<td>No; U</td>
</tr>
<tr>
<td>12</td>
<td>Dehydration</td>
<td>19</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Not for Direct Ingestion (5.8)), PCI, MG</td>
</tr>
<tr>
<td>13</td>
<td>Syncope</td>
<td>18</td>
<td>Yes; W/P (labeled as orthostatic hypotension under Serious Fluid and Serum Chemistry Abnormalities (5.1))</td>
</tr>
<tr>
<td>14</td>
<td>Abdominal pain upper</td>
<td>17</td>
<td>See Row 9—Abdominal pain</td>
</tr>
<tr>
<td>15</td>
<td>Abdominal distension</td>
<td>15</td>
<td>Yes; AR, PCI</td>
</tr>
<tr>
<td>16</td>
<td><strong>Seizure</strong></td>
<td>15</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Seizure (5.2)), AR, DI, MG</td>
</tr>
</tbody>
</table>

Reference ID: 4087114
Table 3. Most Frequently Reported MedDRA PTs with N ≥ 10 for sodium picosulfate/ magnesium oxide/ citric acid, Received by FDA from February 1, 2014 to February 28, 2017, Sorted by Decreasing Number of FAERS Reports per PT

<table>
<thead>
<tr>
<th>No.</th>
<th>PT</th>
<th>Frequency</th>
<th>Nature of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Asthenia</td>
<td>13</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>18</td>
<td>Fall</td>
<td>12</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>19</td>
<td>Muscle spasms</td>
<td>12</td>
<td>No; co-reported with other labeled events such as seizure, dizziness, dehydration</td>
</tr>
<tr>
<td>20</td>
<td>Underdose</td>
<td>11</td>
<td>No; U, co-reported with the PT Drug ineffective</td>
</tr>
<tr>
<td>21</td>
<td>Anorectal discomfort</td>
<td>10</td>
<td>Yes; labeled as proctalgia in AR</td>
</tr>
<tr>
<td>22</td>
<td>Confusional state</td>
<td>10</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>23</td>
<td>Hypokalaemia</td>
<td>10</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Seizure (5.2)), AR, DI</td>
</tr>
<tr>
<td>24</td>
<td>Retching</td>
<td>10</td>
<td>No; co-reported with the PT nausea, which is a labeled event</td>
</tr>
</tbody>
</table>

* A report may contain more than one MedDRA PT.
† Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide or Other Categories: CM = Confounded by Concomitant Medications, DR = Disease-related, IR = Indication-related, PR = Procedure-related, U = Uninformative

Reviewer comment: The majority of the adverse events were labeled events (such as diarrhea, dehydration) or were unlabeled adverse events that occurred in the context of other labeled adverse events (such as retching with nausea, fall with dehydration). Thus, the unlabeled adverse events do not represent new safety signals.
<table>
<thead>
<tr>
<th>Row</th>
<th>MedDRA PT</th>
<th>Number of FAERS Reports†</th>
<th>Labeled (Yes/No), Location or Other Category‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
<td>42</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Not for Direct Ingestion (5.8)), AR, PCI, MG</td>
</tr>
<tr>
<td>2</td>
<td>Hyponatraemia</td>
<td>37</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Seizure (5.2)), AR, DI</td>
</tr>
<tr>
<td>3</td>
<td>Nausea</td>
<td>36</td>
<td>Yes; W/P (Not for Direct Ingestion (5.8)), AR, PCI, MG</td>
</tr>
<tr>
<td>4</td>
<td>Diarrhoea</td>
<td>24</td>
<td>Yes; IR, AR, MG</td>
</tr>
<tr>
<td>5</td>
<td>Loss of consciousness</td>
<td>24</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>6</td>
<td>Headache</td>
<td>23</td>
<td>Yes; AR, MG</td>
</tr>
<tr>
<td>7</td>
<td>Dizziness</td>
<td>21</td>
<td>Yes; AR, MG</td>
</tr>
<tr>
<td>8</td>
<td>Drug ineffective</td>
<td>19</td>
<td>No; U</td>
</tr>
<tr>
<td>9</td>
<td>Malaise</td>
<td>17</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>10</td>
<td>Seizure</td>
<td>15</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Seizure (5.2)), AR, DI, MG</td>
</tr>
<tr>
<td>11</td>
<td>Dehydration</td>
<td>14</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Not for Direct Ingestion (5.8)), PCI, MG</td>
</tr>
<tr>
<td>12</td>
<td>Syncope</td>
<td>13</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>13</td>
<td>Abdominal pain</td>
<td>12</td>
<td>Yes; AR, PCI, MG</td>
</tr>
<tr>
<td>14</td>
<td>Fall</td>
<td>12</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>15</td>
<td>Asthenia</td>
<td>10</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
</tbody>
</table>

Table 4. MedDRA PTs with N ≥ 10 from FAERS Reports with Serious Outcomes* for sodium picosulfate/ magnesium oxide/ citric acid, Received by FDA from February 1, 2014 to February 28, 2017, Sorted by Decreasing Number of FAERS Reports per PT

N=136

Reference ID: 4087114
Table 4. MedDRA PTs with N ≥ 10 from FAERS Reports with Serious Outcomes* for sodium picosulfate/magnesium oxide/citric acid, Received by FDA from February 1, 2014 to February 28, 2017, Sorted by Decreasing Number of FAERS Reports per PT

<table>
<thead>
<tr>
<th>N</th>
<th>MedDRA PT</th>
<th>Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Confusional state</td>
<td>10</td>
<td>No; multiple cases co-reported with other signs and symptoms of dehydration or electrolyte imbalances</td>
</tr>
<tr>
<td>17</td>
<td>Hypokalaemia</td>
<td>10</td>
<td>Yes; W/P (labeled under Serious Fluid and Serum Chemistry Abnormalities (5.1), Seizure (5.2)), AR, DI</td>
</tr>
</tbody>
</table>

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.
† A report may contain more than one MedDRA PT.
‡ Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide or Other Categories: CM = Confounded by Concomitant Medications, DR = Disease-related, IR = Indication-related, PR = Procedure-related, U = Uninformative

Reviewer comment: Similar to the findings from the FDAAA Section 915 NME Postmarket Safety Summary Analysis completed on January 31, 2014, all but one of the reports of hyponatremia, and all reports of seizure had a serious outcome.

Death cases (n=4)
There were four foreign reports of death. Two cases of death were unlikely to be associated with sodium picosulfate/magnesium oxide/citric acid — one described a patient who was hospitalized and died from a cardiac arrhythmia, but there was no evidence that the medication was ever prescribed or administered while the patient was hospitalized; and one with an unknown cause of death also did not report a temporal relationship to drug administration. We are unable to exclude sodium picosulfate/magnesium oxide/citric acid as a contributor to the patient’s death in the two remaining cases, which are summarized below:
3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Hyponatremia (n=39)
Forty-four reports of hyponatremia were identified with the following PTs Hyponaetremia (n=38), Blood sodium decreased (n=5), and Hyponatraemic encephalopathy (n=1). After exclusion of duplicate reports, 39 unique cases of hyponatremia were identified. Thirteen cases were domestic and 26 were foreign. Of the 39 unique cases, 35 were associated with a serious outcome including one death and 32 hospitalizations. Twelve of 32 patients who required hospitalization were admitted to the intensive care unit. Sixteen of 39 cases reported hyponatremia as resolving or resolved, one reported the hyponatremia as not recovered on day 16 of hospitalization, and 22 did not provide information. The patients who experienced hyponatremia had a median age of 68 years, ranging from 26 to 81 years of age (n=30). Thirty-two of 39 cases occurred in female patients, one occurred in a male patient, and the remaining six did not report the patient’s sex. Thirteen of 39 cases reported concomitant administration of medications that may increase the risk for fluid and electrolyte disturbances such as angiotensin receptors blockers, diuretics, selective serotonin reuptake inhibitors, and other laxatives (polyethylene glycol, lactulose). Information on adherence to the dosing regimens and consumption of fluids was lacking in the majority of cases. The median nadir sodium level reported temporal to sodium picosulfate/ magnesium oxide/ citric acid administration in the cases was 117 mEq/L, ranging from 110 to 125 mEq/L (n=19). No cases reported a sodium level prior to receiving the sodium picosulfate/ magnesium oxide/ citric acid. Other events commonly reported in the hyponatremia cases included vomiting (n=17), altered
consciousness (n=15), nausea (n=11), seizures (n=11), hypokalemia (n=8), headache (n=8), malaise (n=8), diarrhea (n=7), amnesia (n=6), dehydration (n=4), and dizziness (n=3).

Reviewer comment: We performed a case-level analysis to determine if there was new safety information to require labeling updates for hyponatremia. We looked for additional risk factors or subgroups that may be more vulnerable to develop hyponatremia, however did not find any new information that differed from what was already included in the label. We also evaluated the cases for the main presenting signs and symptoms of hyponatremia. The two most frequently reported symptoms were vomiting and altered consciousness. Although both of these symptoms would be indicative of dehydration, altered consciousness is not explicitly listed in the product label. Overall, the cases reinforced that the development of hyponatremia after receiving sodium picosulfate/magnesium oxide/citric acid can result in serious adverse events including seizures.

Electrolyte imbalance (n=23)
Twenty-three reports of electrolyte imbalance were identified with adverse events or PTs indicative of electrolyte imbalance: Hypokalaemia (n=10), Electrolyte imbalance (n=5), Blood potassium decreased (n=5), Hypocalcaemia (n=2), Hypochloraemia (n=2), Blood magnesium abnormal (n=1), Blood potassium abnormal (n=1), Hypercalcaemia (n=1), Hypophosphataemia (n=1), and Hypoosmolar state (n=1). Seventeen of the 23 reports documented concomitant hyponatremia, which are analyzed above in the Hyponatremia section. Of the remaining six cases of electrolyte imbalance, five were associated with a serious outcome, of which two resulted in hospitalization. None of the six cases reported use of concomitant medications that may increase the risk for fluid and electrolyte disturbances. Four of six cases reported the development of pre-syncope or syncope and electrolyte imbalance (n=2) or hypokalemia (n=2). One direct case reported the development of headache from a suspected alteration in magnesium, but the alteration in magnesium was not medically confirmed. One case reported the development of atrial fibrillation in conjunction with hypocalcemia.

Reviewer comment: Electrolyte imbalance is currently labeled in the Warnings and Precautions Section 5.1 Serious Fluid and Serum Chemistry Abnormalities of the Prepopik product label. Section 5.1 warns that patients may develop signs of dehydration or electrolyte disturbances that can result in orthostatic changes, cardiac arrhythmias, seizures, or renal impairment. There is no new information in the cases to suggest the need for changes to the current labeling for Prepopik.

Seizures (n=16)
There were 18 reports of seizure (n=15) or generalized tonic-clonic seizure (n=3), of which two were duplicate reports. All 16 unique cases were associated with a serious outcome, of which 13 resulted in hospitalization. Of the 16 cases, one reported the patient had a similar seizure event 30 years prior (triggering factor unknown), one reported the patient did not have a history of seizures, and 14 did not report seizure history. Eleven of 16 cases reported the patient developed hyponatremia with or without additional electrolyte imbalances that contributed to the seizure.

- The cases with altered consciousness were identified with the following PTs: 1) Altered state of consciousness, 2) Confusional state, 3) Depresses level of consciousness, 4) Disorientation, and 5) Loss of consciousness.
- The commonly reported events are not mutually exclusive.
- The events are not mutually exclusive. A report may be associated with more than one PT.
Reviewer comment: Seizure is currently labeled in the Warnings and Precautions section of the Prepopik product label. There is no new information in the cases to suggest the need for changes to the current labeling for Prepopik.

**Ischemic colitis (n=3)**
There were three cases of ischemic colitis reported with use of sodium picosulfate/ magnesium oxide/citric acid, of which two cases had limited information for assessment. The remaining case reported a 69-year-old female patient developed ischemic colitis within 24 hours of receiving PicoPrep (sodium picosulfate/ magnesium oxide/ citric acid); however, the patient also received concomitant sennosides 36 mg and had a past medical history significant for ischemic colitis and positive fecal occult blood tests. 
Reviewer comment: The single case with temporal relationship to PicoPrep administration also received concomitant sennosides, which is a stimulant laxative that may increase the risk for this adverse event. Additionally, the patient had a history significant for ischemic colitis. No new information regarding ischemic colitis and Prepopik was identified from review of the three new cases. Ischemic colitis is appropriately labeled in the Warnings and Precautions Section of the current Prepopik product label.

**Ulcerative colitis flare (n=0)**
There were zero cases reporting the patient had a flare of ulcerative colitis.

4 **CONCLUSION**

A review of all FAERS postmarketing adverse event reports with sodium picosulfate/ magnesium oxide/ citric acid during the February 1, 2014 to February 28, 2017 time interval revealed no new safety issues. Five AESIs were evaluated—hyponatremia, electrolyte imbalance, seizures, ischemic colitis, and ulcerative colitis flare. Although FDA continues to receive reports of hyponatremia, electrolyte imbalance, and seizures with serious outcomes, we did not identify subgroups of patients or risk factors for the development of such events to recommend labeling updates. However, we did identify that altered consciousness was one of the most frequently reported symptoms in the 39 cases of hyponatremia. Although this is a recognized symptom of dehydration, it may be informative to add this symptom to the medication guide to aid in identification of hyponatremia prior to the development of other adverse events, such as seizures. No new information was identified regarding ischemic colitis or ulcerative colitis flare.

5 **RECOMMENDATIONS**

DPV recommends consideration to be given to consulting the Patient Labeling Team in the Division of Medical Policy Programs to determine if the symptom of altered consciousness should be added to the medication guide.
APPENDICES

APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)
The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER

Reference ID: 4087114
7 REFERENCES

1 Carr J. DGIEP consult to OSE/DPV. February 21, 2017. Available at:
2 Cao C. Pharmacovigilance review of PicoPrep and ischemic colitis, electrolyte imbalance, flare of ulcerative
3 Korvick J, Levin RL. FDAAA section 915 new molecular entity postmarket safety summary for Prepopik. June 16,
4 Prepopik (sodium picosulfate, magnesium oxide, and anhydrous citric acid) [package insert]. Parsippany, NJ:
   Ferring Pharmaceuticals Inc.; Label revised April 2015.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M HARINSTEIN
04/20/2017

EILEEN WU
04/20/2017

MONICA MUNOZ
04/20/2017

Reference ID: 4087114