UNIFIED CLINICAL/STATISTICAL REVIEW

Application Type	NDA
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Priority or Standard	Standard
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Division/Office	DGIEP/OND
Reviewer Name(s)	Erica Lyons, MD
Review Completion Date	August 9, 2018
Established/Proper Name	Prepopik
(Proposed) Trade Name	Prepopik
Applicant	Ferring Pharmaceuticals Inc.
Dosage Form(s)	Sachet, powder for oral solution
Applicant Proposed Dosing Regimen(s)	1 sachet x 2 doses
Applicant Proposed Indication(s)/Population(s)	Cleansing of the colon as a preparation for colonoscopy in patients ≥ 9 years of age
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Cleansing of the colon as a preparation for colonoscopy in patients ≥ 9 years of age

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OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

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Glossary

AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

sNDA 202535, by Ferring Pharmaceuticals seeks the approval of Prepopik in pediatric patients ≥ 9 years of age. Prepopik (sodium picosulfate, magnesium oxide, and citric acid) powder for oral solution is currently indicated for cleansing of the colon as a preparation for colonoscopy in adults.

Prepopik is dispensed in a carton that contains 2 sachets, each holding a total of either 16.1 g (orange flavor) or 16.2 g (cranberry flavor) of powder for oral solution. Each sachet contains sodium picosulfate 10 mg, magnesium oxide 3.5 g, and anhydrous citric acid 12.0 g. The recommended bowel cleansing preparation is 2 sachets taken prior to colonoscopy. The magnesium oxide and citric acid components form the equivalent of a magnesium citrate solution when the powder is dissolved in water.

Sodium picosulfate/magnesium citrate acts to clear the colon and rectum of fecal contents as both a stimulant laxative, by increasing the frequency and the force of peristalsis (picosulfate metabolite), and an osmotic laxative by retaining fluids in the colon (magnesium citrate component).

Prepopik is available in an identical formulation for adults. Dosing regimens include the "split-dose" (preferred) or the "day-before" (alternative) regimens, with timing relative to colonoscopy as described in the current label.[1] Split dosing is the preferred method as it may enhance efficacy (data suggest that colonoscopies performed within 6-8 hours after the preparation were associated with significantly better bowel cleansing than those performed more than 8 hours after the end of the preparation[2]), while minimizing the risk of dehydration associated with bowel preparations.

<u>"Split-Dose" Dosage Regimen (Preferred Method)</u>

-First dose: administer one sachet during evening before the colonoscopy

[1] Prepopik- Approved Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202535lbl.pdf
[2] Marmo et al. Effective bowel cleansing before colonoscopy: a randomized study of split dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions Gastrointestinal Endoscopy Volume 72, No.2: 2010.

-Second dose: the second sachet is taken the next day, during the morning prior to the colonoscopy

"Day-Before" (Alternative Method)

-First dose: the first sachet is taken during afternoon or early evening before the colonoscopy

-Second dose: the second sachet is taken 6 hours later during evening before colonoscopy

Additional clear liquids (no solid food or milk) must be consumed after every dose in both dosing regimens. Five 8-ounce drinks are to be consumed after the first dose, and three 8-ounce drinks are to be consumed after the second dose.

Because Prepopik is a combination drug product of the active pharmaceutical ingredients of sodium picosulfate, magnesium oxide, and anhydrous citric acid, this sNDA is a 505(b)(2) application[3] due to reliance on literature to support the contribution of each component of the combination. This is discussed further in section 3.2 Summary of Presubmission/Submission Regulatory Activity below.

Development of a premixed solution formulation of the product by the Applicant was approved under NDA 209589 (Clenpiq) on November 28, 2017.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This pediatric trial for Prepopik was adequate and well-controlled given the inherent difficulty in establishing a noninferiority margin relative to placebo for bowel cleaning products due to the lack of placebo-controlled data, (discussed further below in section 7.3 Integrated Assessment of Effectiveness) and the limited sample size available for study. Patients 9-12 years of age were randomized to Prepopik ½ sachet x 2 doses, Prepopik 1 sachet x 2 doses, or the comparator polyethylene glycol (PEG) per standard of care. Patients 13-16 years of age were randomized to either Prepopik 1 sachet x 2 doses or PEG per standard of care. The observed success rate, as defined by "excellent" or "good" on the Aronchick scale, for the dosage regimen consisting of Prepopik 1 sachet x 2 was similar to that of the comparator, PEG, in both the 9-12-year age group (87.5% and 81.3%, respectively) and the 13-16-year age group (81.3% and 85.7%, respectively). This performance, in combination with partial extrapolation from efficacy in adult populations, is supportive of a positive assessment of efficacy for Prepopik at a dose of 1 sachet x 2 for pediatric patients 9 years of age and older, despite the uncertainty

[3] NDA 202535, CDTL review dated 07/14/2012 by Dr. Robert Fiorentino.

created by the wide confidence intervals seen during analysis of the study data. The alternate dosage of Prepopik studied in patients 9-12 years of age, ½ sachet x 2, did not demonstrate comparable efficacy to the comparator, PEG. The doses of ½ sachet x 2 and 1 sachet x 2 were selected for Study 000103 based on the effective adult dose and a literature review of clinical trials of Prepopik products in pediatric patients, as shown in Table 3 below.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Colonoscopy is the current standard method for diagnostic exploration and therapeutic procedures of the colon in both children and adults. Adequate preparation of the bowel with elimination of fecal material is necessary to ensure adequate visualization. There are several FDA-approved bowel cleansing preparations, including osmotic laxatives, stimulant laxatives, or combination osmotic/stimulant products. Of these, Nulytely is approved for use in pediatric patients. Although pediatric dosing in ml/kg/hr is described in the product label, in clinical practice many non-standardized pediatric bowel preparation dosing regimens are used. Colon cleansing products should be easy to use, well-tolerated, and safe, with few adverse effects (AEs) and minimal shifts in the patient's fluid and electrolyte balance, as most often these preparations are taken prior to the colonoscopy in an outpatient setting. This is especially important for products for pediatric patients, as they may be more sensitive to such shifts and thus more likely to develop clinical symptoms.

Prepopik is a combination osmotic/stimulant preparation containing sodium picosulfate, magnesium oxide, and citric acid and is currently approved for cleansing of the colon as a preparation for colonoscopy in adults. This sNDA is a 505(b)(2) application due to reliance on literature to support the contribution of each component of the combination product. It was evaluated in an adequate and well-controlled trial including patients 9-16 years of age, in which the observed success rate as defined by "excellent" or "good" on the Aronchick scale for Prepopik 1 sachet x 2 was similar to the comparator, PEG, in both the 9-12-year age group (88% and 81%, respectively) and the 13 to 16-year age group (81% and 86%, respectively). The alternate dosage of Prepopik studied, ½ sachet x 2, did not demonstrate comparable efficacy to the comparator, PEG, in subjects 9-12 years of age (50% and 81%, respectively).

The study was limited by the inherent difficulty in establishing a noninferiority margin relative to placebo for bowel cleaning products due to the lack of placebo-controlled data and the limited sample size available for study. Additionally, no formal statistical tests were planned. The treatment group difference was assessed by constructing the 90% and 95% confidence intervals (CIs) of the difference in proportions between each Prepopik cohort and PEG cohort by age group. Although the reported CIs are wide, additional support for the efficacy of Prepopik in patients 9 years of age and older is provided by partial extrapolation from efficacy in adult populations.

The risks seen with Prepopik within this pediatric trial are similar to those observed and further characterized within the clinical trials conducted in the adult population. The most common adverse reactions (>1%) currently listed within the product label for Prepopik are nausea, headache and vomiting. Additionally, serious fluid and serum electrolyte abnormalities, seizures secondary to fluid/electrolyte

disturbances, increased risk for renal injury in patients with renal impairment, and rare reports of cardiac arrhythmias are reported in the current Warnings and Precautions section of Prepopik labeling.

The most common adverse reactions (>5%) seen with Prepopik during this trial were nausea and vomiting. Significant shifts of serum magnesium (consistent with ingestion of the magnesium citrate component) and glucose (consistent with a known class effect of ingestion of a noncaloric product during a time of pre-procedure fasting) were seen in pediatric patients. No subject had a reported magnesium value that exceeded the standard definition of hypermagnesemia or clinical symptoms associated with elevated magnesium levels; however, magnesium values were not recorded for all patients including a subject with an AE of lethargy as discussed further below. Review of subjects with markedly abnormal glucose revealed three cases from the 78 subjects studied. Two of these subjects were treated with Prepopik 1 sachet x 2 and one received PEG. The abnormal values occurred at the 5 Day follow-up visit for two subjects (PEG and Prepopik 1 sachet x 2) and at the colonoscopy visit for the remaining subject (Prepopik 1 sachet x 2). There were no adverse events associated with the abnormal glucose values, and per report all three patients were asymptomatic at the time of the event. The occurrence of significant hypoglycemia (2.2-2.6 mmol/L = 40-47 mg/dL) in conjunction with the potential for off-label use in younger populations is supportive of inclusion of a description of the potential for hypoglycemia within Pediatric Use section in the product labeling.

Orthostasis was seen more often in those treated with Prepopik (~20%) than PEG (~7%). This finding was most pronounced among patients 9 to 12 years of age treated with Prepopik 1 sachet x 2 (~24%). These changes occurred at similar rates in both the ½ sachet x 2 and 1 sachet x 2 treatment groups and were noted to occur up to 5 days following Prepopik administration. As with serum magnesium shifts, missing data did not allow for a complete exclusion of clinical symptoms associated with this finding. Although discussion of orthostatic changes seen in adults is currently included in the product label, considering these pediatric findings, it is appropriate to include a description of the orthostatic changes seen in the pediatric study to the Warnings and Precautions section of the product labeling.

On evaluation of the pharmacodynamic properties of Prepopik in patients 9 years of age and older, a 1.9-fold increase in exposure was noted compared to the adult population after administration of the same dose. The increased exposure was not associated with corresponding adverse events in subjects where exposure data was captured within the trial or in exposure-response analyses conducted by the clinical pharmacology reviewers for orthostatic changes as the primary AE of interest.

Overall, the benefit-risk profile for Prepopik appears favorable for pediatric patients ages 9 and above.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Colonoscopy is the standard method for diagnostic and therapeutic procedures of the colon in pediatric and adult patients. • For a colonoscopy to be successfully performed, adequate bowel preparation is necessary to eliminate fecal contents and ensure visibility. • Inadequate preparation can result in missed findings or diagnoses, increased exposure to sedation medications, and need to reschedule or repeat the procedure.	Effective bowel preparation is essential for the diagnostic and therapeutic functions of colonoscopy.
Current Treatment Options	• There are several FDA-approved products indicated for cleansing of the colon prior to colonoscopy including osmotic, stimulant, and combination osmotic/stimulant preparations. • Of available products, only Nulytely (and the generic Trilyte) has been approved for use in pediatric patients. • In clinical practice, Nulytely is administered in several nonstandard pediatric dosing regimens.	There is a need for well-tolerated, safe, and efficacious pediatric bowel preparations with clear dosing administration guidelines.
Benefit	• The application contains data from a clinical trial in which patients 9-16 years of age underwent bowel preparation and colonoscopy. • The effectiveness of Prepopik was established for patients 9 and older in Study 000103, a multicenter, randomized, double-blind, active comparator study conducted in the US. The study population consisted of 78 pediatric patients 9-16 years of age undergoing diagnostic colonoscopy. PEG was selected as the active comparator	The application has established that Prepopik at a dose of 1 sachet x 2 is effective for cleansing of the colon in preparation for colonoscopy, as it demonstrated similar performance to the comparator product in achieving “excellent” or “good” results on the Aronchick scale. “Excellent” or “good” results

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and administered per the standard of care at the respective study site. Two age cohorts were assessed, 9-12 years old and 13-16 years old. Within the 9-12 year cohort, two doses of Prepopik were studied, 1 sachet x 2 and ½ sachet x 2. Efficacy was evaluated by assessing the observed success rate as defined by "excellent" or "good" on the Aronchick scale and comparing that to the observed success rate for the comparator, PEG. Prepopik at a dose of 1 sachet x 2 performed similarly to PEG in both the 9-12 year age group (87.5% and 81.3%, respectively) and the 13 to 16 year age group (81.3% and 85.7%, respectively). The alternate dose of Prepopik studied in the 9-12 year age group, ½ sachet x 2, did not demonstrate comparable efficacy (50%). • Studies of bowel preparations are limited by the lack of placebo control. • Additional challenges to the interpretation of Study 000103 include: small sample size, presence of wide confidence intervals, and lack of pre-specified formal statistical analysis.	on this scale are considered to indicate successful preparation to allow for completion of a colonoscopy. There is sufficient evidence to support a recommendation for approval of the 1 sachet x 2 dosage for patients ages 9 and above. Approval for the ½ sachet dosing is not recommended. Lack of placebo control is acceptable for studies of bowel preparations, as no "placebo effect" on efficacy is expected. The evidence of efficacy for Prepopik in adults is supportive of the determination of efficacy for pediatric patients, as the mechanism of action is age-independent. This partial extrapolation, in conjunction with the positive efficacy assessment for the 1 sachet x 1 dosing, outweighs the uncertainties created by lack of placebo control, small sample size, wide confidence intervals, and lack of pre-specified formal statistical analysis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The risks of Prepopik observed in Study 000103 are similar to those established in pre-and post-marketing experience with Prepopik in adult populations. The most common adverse reactions (>5%) were nausea and vomiting. These, along with headache, are the most common adverse reactions (>1%) currently described in the Prepopik label. • Fluid and electrolyte abnormalities are a class effect of bowel preparations. Significant shifts in serum magnesium were seen with Prepopik due to ingestion of the magnesium citrate component. Although numerically significant, the shifts did not reach levels known to have clinical significance and were not associated with adverse events; however, missing data did not allow for complete certainty in this assessment. • Ingestion of a noncaloric product during pre-procedure fasting has been associated with hypoglycemia in pediatric patients. • Three cases of significant hypoglycemia were seen during Study 000103. Of these 2 occurred at the 5 Day follow-up visit, and one with the comparator product, PEG. • An imbalance in the presence of orthostatic changes was observed between Prepopik and PEG.	The risks of Prepopik treatment in pediatric patients are largely consistent with the established safety profile of Prepopik in adults. Although discussion of orthostatic changes seen in adults is currently included in the product label, additional discussion of the orthostatic changes seen in pediatric patients should be included in the label. The occurrence of significant hypoglycemia and the potential for off-label use in younger populations is supportive of inclusion of a description of the potential for hypoglycemia within the product label. The risks observed with Prepopik administration to patients 9 years of age and older can be managed by appropriate labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that were submitted as part of the application include:							Section where discussed, if applicable
	x □	Clinical outcome assessment (COA) data, such as						
			x □	Patient reported outcome (PRO)				000103 Clinical Study Report, Section 9.2.1
			□	Observer reported outcome (ObsRO)				
			x □	Clinician reported outcome (ClinRO)				000103 Clinical Study Report, Section 9.1
			□	Performance outcome (PerfO)				
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)						
	□	Patient-focused drug development or other stakeholder meeting summary reports						
	□	Observational survey studies designed to capture patient experience data						
	□	Natural history studies						
	□	Patient preference studies (e.g., submitted studies or scientific publications)						
	□	Other: (Please specify)						
□	Patient experience data that were not submitted in the application, but were considered in this review:							
			□	Input informed from participation in meetings with patient stakeholders				
			□	Patient-focused drug development or other stakeholder meeting summary reports				
			□	Observational survey studies designed to capture patient experience data				
			□	Other: (Please specify)				
□	Patient experience data was not submitted as part of this application.							

2. Therapeutic Context

2.1. Analysis of Condition

Colonoscopy is the current standard method for diagnostic exploration and therapeutic procedures of the colon in both children and adults. Adequate preparation of the bowel with elimination of fecal material is necessary to ensure adequate visualization of the colon. Inadequate preparation may lead to a decreased detection rate of abnormal findings such as adenomas, polyps, or colorectal cancers, as well as increased duration of the procedure or need for repeated evaluation, which may in turn increase the risk of complications and cost.[4,5,6] Pediatric indications for colonoscopy include:

- Lower gastrointestinal hemorrhage (anal fissure, colitis, benign juvenile polyps, vascular malformations such as hemangiomas or telangiectasias, internal hemorrhoids)
- Chronic diarrhea with a history suggestive of chronic colitis or ileitis
- Acute or chronic colitis
- Suspected inflammatory bowel disease
- Suspected polyposis syndrome
- Cancer surveillance in children with polyposis syndromes or chronic ulcerative colitis
- Polyp removal
- Foreign body removal
- Stricture dilation
- Decompression of obstructed colon[7]

No standardized pediatric bowel preparation regimen exists. PEG-based solutions are most commonly used in clinical practice.[8]

[4] Lebwohl B, Kastrinos F, Glick M, Rosenbaum AJ, Wang T, Neugut AI. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. Gastrointest Endosc. 2011;73(6):1207-14.

[5] Rex DK, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and cost of colonoscopy. Am J Gastroenterol 2002; 97: 1696-1700.

[6] Wexner SD, Beck DE, Baron TH, Fanelli, RD, Hyman N, Shen B, et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Surg Endosc. 2006; 20:1147-60.

[7] Pediatric Gastrointestinal Imaging and Intervention: Volume 1. 2nd Edition. Stringer D.A. and Babyn P.S., B.C. Decker Inc., 2001.

[8] Hunter A and Mamula P. Bowel preparation for pediatric colonoscopy procedures. Journal of Pediatric Gastroenterology and Nutrition 51: 254-261, 2010.

Bowel preparations should clear the colon of all solid material without damaging the colonic mucosa. It is important that colon cleansing products be easy to use, well-tolerated, and safe, with few adverse effects and minimal shifts in the patient's fluid and electrolyte balance, as most often these preparations are taken prior to the colonoscopy in an outpatient setting.

Compounds currently used for bowel cleansing can be divided into 3 categories according to their mechanism of action: isosmotic, hyperosmotic, and stimulant.[9]

Isosmotic preparations

Preparations that contain PEG are considered osmotically balanced, high volume, non-absorbable, and non-fermentable electrolyte solutions. These solutions cleanse the bowel with less water and electrolyte shifts and provide evacuation primarily by the mechanical effect of large-volume lavage. With sodium sulfate preparations, sodium absorption in the small intestine is reduced due to the absence of chloride, the accompanying anion necessary for active absorption against an electrochemical gradient. Low-volume PEG preparations are used in combination with stimulant laxatives or ascorbic acid.

Hyperosmotic preparations

These preparations draw water into the bowel lumen, which stimulates peristalsis and evacuation. These are smaller-volume preparations but their hyperosmotic nature can cause fluid shifts, accompanied by transient serum electrolyte alterations. Magnesium citrate is a hyperosmotic agent with additional effects through release of cholecystokinin, resulting in fluid secretion and stimulation of peristalsis. Magnesium citrate is often used in combination with other agents due to decreased efficacy when given alone.

Stimulant preparations

Stimulant laxatives promote colonic motility through variable mechanisms that are incompletely characterized. Bisacodyl is a diphenylmethane derivative that is poorly absorbed in the small intestine and hydrolyzed by endogenous esterases. Its active metabolites stimulate colonic motility, with an onset of action between 6 and 10 hours. Sodium picosulfate is a member of a series of phenolester compounds (including bisacodyl) with potent locally-acting stimulant laxative properties. The cathartic activity of both bisacodyl and sodium picosulfate depends on the conversion to an active metabolite, bis-(p-hydroxyphenyl)-pyridyl-2-methane or BHPM. Senna, an anthracene derivative, is processed by colonic bacteria to its active metabolite to stimulate colonic peristalsis. Senna, in combination with a liquid diet, has been used as a colon cleansing agent in children.

[9] Information on bowel prep categories adapted from Dr. Zana H. Marks, MD's primary clinical review of NDA 202535.

2.2. Analysis of Current Treatment Options

There are currently several products approved by the U.S. FDA for colon cleansing as a preparation for colonoscopy, as summarized in Table 1.

Table 1. Currently Available Therapies for Colon Cleansing as a Preparation for Colonoscopy

Class	Generic Name	Brand Name	Formulation	Approved Ages
Osmotic Laxatives	Polyethylene Glycol Electrolyte Solution	Moviprep	Powder	18 +
	Sodium Bisphosphate/Sodium Phosphate	Osmoprep	Tablet	18 +
	Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate	Suprep	Solution	18 +
	Polyethylene Glycol and Electrolytes for Oral Solution	Nulytley	Powder	6 months +
	Polyethylene Glycol and Electrolytes for Oral Solution	Trilyte	Powder	6 months +
	Polyethylene Glycol Electrolyte Solution	Golytely	Powder	18 +
	Polyethylene Glycol Electrolyte Solution	Colyte	Powder	18 +
	Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate	Colprep Kit	Powder	18 +
Combination Osmotic/Stimulant Laxatives	Monobasic sodium phosphate and dibasic sodium phosphate	Visicol	Tablet	18 +
	Polyethylene Glycol with Electrolytes & Bisacodyl	HalfLytely & Bisacodyl	Powder/Tablet	18+
	Sodium Picosulfate, Magnesium Oxide, & Citric Acid	Prepopik	Powder	18+

Source: Erica Lyons, MD FDA Medical Officer from: drugs@fda: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed 11/3/2017

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Prepopik powder for oral solution was approved on July 16, 2012 under NDA 202535 (Ferring Pharmaceuticals Inc.) as indicated for cleansing of the colon as a preparation for colonoscopy in adults.

3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory interactions are listed below by date. Points of discussion of Division recommendations are provided as a bulleted list for each meeting. The development program for Prepopik occurred under IND 101738.

September 16, 2011: NDA 202535 was submitted for review.

- Major Efficacy Review Issues:
  - Fulfillment of the combination rule using literature under 505 (b)(2)
  - Inclusion of the alternative "Day Before" dosing regimen in the labeling
- Major Safety Review Issues:
  - Consideration of a post-marketing safety trial based on eGFR, creatinine, and other laboratory data
  - Screening for evidence of ischemic colitis given the active metabolite of the picosulfate component of the product is the same as that of the bisacodyl component of the HalfLytely and Bisacodyl 10 mg Tablets Bowel Prep Kit no longer marketed due to safety concerns related to ischemic colitis
- Pediatric Development Plan[10]

May 30, 2012: Pediatric study plan reviewed at PeRC.

- Partial waiver in pediatric patients less than 6 months of age to be consistent with the comparator
- Step-wise approach to trials by age group

July 11, 2012: Revised Pediatric Plan discussed at PeRC.

- Addition of dose-ranging component and active control to protocol

[10] NDA 202535 Division Director Review. Donna Griebel, MD. July 16, 2012.

- Revision of the age ranges for the waiver and deferral requests to less than 1 year of age
- Eligibility criteria revised

July 16, 2012: Prepopik was approved for use in adults as indicated for cleansing of the colon as a preparation for colonoscopy. During the review, it was determined that the "Day Before" alternate dosing regimen was acceptable for inclusion in the label. No additional commitments regarding screening for evidence for ischemic colitis were required post-approval. The following studies and timelines were required per the NDA Approval letter:

1902-1 Conduct a randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 9 years to 16 years). This study will include PK assessments.

- Final protocol submission: February 2013
- Study completion: February 2016
- Final report submission: August 2016

Reviewer Comment:
Ferring Protocol 000103 was submitted to IND 101738 on February 8, 2013. Prior to this the pediatric development plan was reviewed at PERC on May 30, 2012 and July 11, 2012 as above.

1902-2 Conduct a randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 2 years to <9 years). This study will include PK assessments.

- Final protocol submission: February 2016
- Study completion: February 2019
- Final report submission: August 2019

1902-3 Conduct a randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 12 months to 2 years). This study will include PK assessments.

- Final protocol submission: February 2018
- Study completion: February 2019
- Final report submission: August 2020

Reviewer Comment:
After review, protocols for pediatric studies mandated as postmarketing requirements (PMRs) 1902-2 and 1902-3 above were combined to a single proposed study in patients ages 12 months to < 9 years. This protocol was submitted on February 24, 2016.

1902-04 Conduct a retrospective study to identify the risk factors associated with development of persistent deterioration of renal function in patients undergoing colon cleansing with Prepopik in preparation for colonoscopy.

- Fulfilled: September 2014

November 23, 2015: A request for Deferral Extension due to difficulty with recruitment for the younger age group (9-12 years) and completing the PK sampling plan was submitted for Study 1901-1.

January 6, 2016: The Deferral Extension request was reviewed by PeRC. Concerns were raised regarding the adequacy of the proposed timeline to meet enrollment goals. PeRC agreed with the Division's decision to deny the request and recommended the Applicant pursue additional sites for enrollment.

January 07, 2016: The request was denied. The Applicant was advised to resubmit the request closer to the deadline as to have a more realistic goal date.

February 16, 2016: Interim PK data were submitted

April 15, 2016: A second request for extension with revised timeline was submitted.

May 27, 2016: A 13-month Pediatric Deferral Extension was granted for study 1901-1.

Revised timeline:

1902-1 Conduct a randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 9 years to 16 years). This study will include PK assessments.

- Final Protocol Submission: February 2013
- Study completion: June 2016
- Final report submission: September 2017

October 2, 2017: sNDA 202535 was submitted as a labeling supplement, based on the results of Study 1902-1 (PMR 1902-1).

October 13, 2017: The labeling supplement submission was withdrawn based on Agency advice.

October 16, 2017: sNDA 202535 was resubmitted as an efficacy supplement. See further discussion of the status of PMR 1902-1 in Section 8.8.3.

Prepopik is a combination drug product of the active pharmaceutical ingredients of sodium picosulfate, magnesium oxide, and anhydrous citric acid. Under 21 CFR 300.50, applicants are required to provide evidence that each component of the combination contributes to the claimed effects of the product, which often entails conduct of a factorial study(ies). This was addressed during the initial review of Prepopik (NDA 202535). The Applicant's reliance on literature to support the lack of need for factorial studies and thus fulfill the requirements of the combination rule was deemed acceptable at the time of review. The reliance on literature classifies this supplement NDA as a 505(b)(2) application.[11]

Exclusivity:

The Applicant has requested 3 years of exclusivity for the proposed label change under 21 CFR314.108(5) (b) (4)

Per the Division of Pediatric and Maternal Health, although Prepopik would be eligible for 3 years of exclusivity for the proposed label change, (b) (4)

3.3. Foreign Regulatory Actions and Marketing History

The investigational product Prepopik was approved for pediatric dosing in children ≥ 1 year of age in the UK (under the name Picolax) in 1985 with dosing based an unpublished study by Dr. J. Ratcliffe,[12] a consultant for the Pediatric Radiologist Department of Radiodiagnosis, Booth Hall Children's Hospital, Manchester, UK.

Prepopik was approved in Canada for children ≥ 1 year of age as Pico-Salax[13] in 2004.

[11] NDA 202535, CDTL review dated 07/14/2012 by Dr. Robert Fiorentino.

[12] Re: Picolax in children. Letter from Dr. John Ratcliffe dated 11 February 1985.

[13] PICO-SALAX® magnesium oxide, citric acid and sodium picosulfate. Powder for oral solution. Purgative [prescribing information]. North York, Ontario, Canada: Ferring Pharmaceuticals; May 26, 2014.

In April 2010 under the Mutual Recognition Procedure, Picolax was also approved in the participating 24 European Economic Area countries on the basis of "well-established use."[14] As of the most recent Development Safety Update Report, March 1, 2018, Ferring's sodium picosulfate, magnesium oxide, and citric acid powder for oral solution products are approved in a total of 74 countries for the following indications: emptying the bowel; cleaning the bowel prior to surgery when judged clinically necessary; cleaning the bowel prior to X-ray examination or endoscopy; cleaning the bowel prior to X-ray examination or endoscopy in adults, adolescents and children from the age of 1 year; cleaning the bowel prior to surgery when judged clinically necessary in adults, adolescents and children from the age of 1 year; or cleaning the colon as a preparation for colonoscopy in adults. These products are not intended for use as a routine laxative.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The report from Drs. Susan Leibenhaut, Susan Thompson, and Kassa Ayalew describes the findings from inspections of three clinical investigator sites. Inspections at all sites have the final classifications of Voluntary Action Indicated. Data generated by Sites 101 and 106 were considered reliable; however, it was recommended that the efficacy data from subjects (b) (6) to (b) (6) at site 103 be excluded from the analysis because of uncertainty about reconstructing the procedures for completing these source documents. This is addressed further below in section 7.1.1 Subpopulations. Additionally, safety follow-up was not conducted per protocol for at least five subjects from Site 103. These subjects have not been eliminated from the safety analysis below given the concern that important safety data may be missed with their exclusion.

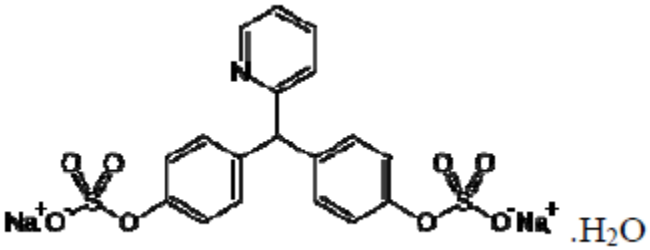
4.2. Product Quality

The CMC reviewers Drs. Le Zhang and David Lewis recommended this supplement for approval from a CMC standpoint.

Sodium picosulfate (stimulant):

[14] Public Assessment Report. Mutual Recognition Procedure. Picolax Powder for Oral Solution. MR: no: UK/H/1960/001/MR. UK license no: PL 03194/0014. Applicant: Ferring Pharmaceuticals Limited. Available at http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con137670.pdf. Accessed 11/9/2017.

- Chemical name 4,4´-(2-pyridylmethylene) diphenyl bis (hydrogen sulfate) disodium salt, monohydrate
- Chemical formula: C18H13NNa2O8S2.H2O
- Molecular Weight: 499.4 g/mol
- Structural formula:



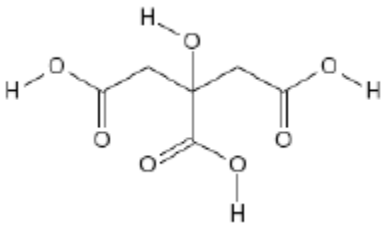
Magnesium citrate (osmotic, formed in solution by the combination of magnesium oxide and anhydrous citric acid):

Magnesium oxide

- Chemical name: magnesium oxide
- Chemical formula: MgO
- Molecular Weight: 40.3 g/mol
- Structural formula: MgO

Anhydrous citric acid

- Chemical name: 2-hydroxypropane-1,2,3-tricarboxylic acid
- Chemical formula: C6H8O7
- Molecular Weight: 192.1 g/mol
- Structural formula:



4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The non-clinical reviewers Drs. Tamal Chakraborti and Sushanta Chakder concluded that from a nonclinical perspective, there are no approvability issues. Labeling comments pertaining to Section 8.1 Pregnancy were conveyed to the Applicant. The Applicant did not submit nonclinical study reports or information for this supplement. Please refer to the May 14, 2012 pharmacology review of NDA 202535 by Dr. Chakraborti for additional details.[15]

4.5. Clinical Pharmacology

The Division of Clinical Pharmacology-3 and the Division of Pharmacometrics in the Office of Clinical Pharmacology have found the submission acceptable from a clinical pharmacology perspective.

4.5.1 Mechanism of Action

The active drug substances in each pouch of PICOPREP are sodium picosulfate (10 mg), a stimulant cathartic, plus magnesium oxide (3.5 g) and citric acid (12 g), which upon mixing with water, form magnesium citrate, an osmotic laxative. The activity of these therapeutically active components is well-established. Sodium picosulfate (4,4´- [2- pyridylmethylene] diphenyl bis [hydrogen sulfate] disodium salt), as a stimulant cathartic, acts on the nerve endings in the colon to induce peristalsis. This purgative effect, however, is exerted only after hydrolysis of picosulfate, by colonic bacteria, to the active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane (BHPM). Sodium picosulfate is reported to take between 6 and 10 hours to exert its full effect. Magnesium citrate, as an osmotic laxative, acts in both the small and large intestine to increase the bulk of the intestinal contents by causing the retention of water within the intestinal lumen. A possible additional action on cholecystokinin, which may increase intestinal fluid and electrolyte accumulation, has been reported. Magnesium citrate has a rapid effect, producing a semi-liquid stool in approximately 3 hours. Thus, the combination of these 2 therapeutically active components produces an efficient dual-action cleansing effect, enabling enhanced visibility for colonoscopy without mucosal harm.

4.5.2 Pharmacodynamics

The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a dual-action purgative effect which, when ingested with additional fluids, produces watery diarrhea.

[15] NDA 202535, Pharmacology/Toxicology review dated 05/14/2012 by Dr. Tamal Chakraborti

4.5.3 Pharmacokinetics

Sodium picosulfate, which is a prodrug, is converted to its active metabolite, BHPM, by colonic bacteria. After administration of 2 pouches of PICOPREP separated by 6 hours, in 16 healthy volunteers, picosulfate reached a mean Cmax of 3.2 ng/mL at approximately 7 hours (Tmax). After the first pouch, the corresponding values were 2.3 ng/mL at 2 hours. The terminal half-life of picosulfate was 7.4 hours. The fraction of the absorbed sodium picosulfate dose excreted unchanged in urine is 0.11%. Plasma levels of the free phenol BHPM were consistently low and urinary samples show that the majority of excreted BHPM was the glucuronide-conjugated form. Magnesium oxide and citric acid react to create magnesium citrate, which is only minimally absorbed from the gastrointestinal tract. Peak raw magnesium concentration (Cmax) was approximately 1.9 mEq/L and occurred at 10 hours post-initial pouch administration (Tmax).[16]

On evaluation of the properties of Prepopik in patients 9 years of age and older, a 1.9-fold increase in exposure was noted compared to the adult population after administration of the same dose. The increased exposure was not associated with corresponding adverse events in subjects where exposure data was captured within the trial or on exposure-response analyses conducted by the clinical pharmacology reviewers for orthostatic changes as the primary AE of interest.

Reviewer Comment:
Although the increased exposure in pediatric patients compared to adults was not related to an increase in adverse events in Study 000103, it should be included in the product labeling.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

[16] Information on mechanism of action, pharmacodynamics, and pharmacokinetics adapted from Dr. Zana H. Marks, MD's primary clinical review of NDA 202535.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2. Listing of Clinical Trial Relevant to sNDA 202535

Trial Identifiers	**Ferring Study 000103, PMR 1902-1, NCT01928862**
Trial Design	Randomized, Multicenter, Assessor-Blind, Dose-Ranging, Parallel Assignment to Active Comparator, Outcome and Safety Study
Regimen/Schedule/Route	Subjects 9-12 years of age were randomized into 3 arms: • Prepopik ½ sachet x 2 doses • Prepopik 1 sachet x 2 doses • PEG per standard of care Subjects 13-16 years of age were randomized into 2 arms: • Prepopik 1 sachet x 2 doses • PEG per standard of care Whether to use the preferred "split-dose" or alternative "day before" method for those in the Prepopik group was deferred to investigator discretion.
Study Endpoints	Primary Endpoint: • Percent of subjects given Prepopik with a bowel preparation rated as excellent or good by Aronchick scale at colonoscopy as compared to those given standard of care, PEG Secondary Endpoints: • Safety • Tolerability and satisfaction • PK • Completion of bowel preparation
Treatment Duration/Follow Up	Treatment Duration: • Treatment began on day prior to procedure and continued to day of procedure for "split-dose" Prepopik • Treatment began and completed on day prior to procedure for "day before" Prepopik and comparator, PEG Trial Duration: Screening - 28-day post treatment follow up
Number of Patients Enrolled	Of 80 patients screened, 78 were enrolled
Study Population	Pediatric subjects ages 9-16 requiring colonoscopy
Number of Centers and Countries	Nine centers across the US participated
Study Duration	June 3, 2014 – March 16, 2017

Source: Erica Lyons, MD FDA Medical Officer from Applicant submitted Clinical Overview and clinicaltrials.gov

Table 3. Literature Review of Clinical Trials of Prepopik Products* in Children

Source	Product, Dose, and Administration	N	Major Efficacy Findings	Major Safety Findings
Evans 1989	Picolax: 2 doses, ~15 hours and 3 hours before procedure 1-4 years: ¼ sachet ×2 4-6 years ½ sachet ×2 > 6 years: 1 sachet ×2	412	Successful examination of colon in 91% of 534 procedures	No major safety issues.
Pinfield 1999	Picolax: 2 doses, 24 hours and 18 hours before procedure <2 years: ¼ sachet ×2 2-5 years: ½ sachet ×2 5-10 years: 1 sachet + ½ sachet >10 years: 1 sachet ×2 Comparator: Bisacodyl/Phosphate enema	63	Bowel preparation was good or excellent in all of the patients in the Picolax group (n = 32) compared with 22 patients in the bisacodyl/phosphate enema group (n = 31).	Vomiting in 3 children in the Picolax group.
Kawakami 2004	Pico-Salax: 2 doses on consecutive days 1-6 years: ¼ sachet ×2 6-12 years: ½ sachet ×2 12-18 years: 1 sachet ×2 Comparator: Magnesium citrate	46	Bowel preparation excellent in 41.3%; good in 52.2%; fair in 6.5%; and poor in 0%.	Side effects in 47.8%, including abdominal cramps (with or without headache), nausea, anal pain and "soiling"
Jimenez-Rivera 2009	Sodium picosulfate/magnesium citrate: 2 doses, 1 hour before breakfast and 2 hours after lunch day before procedure 1-2 years: ¼ sachet ×2 2-4 years: ½ sachet ×2 4-9 years: 1 sachet + ½ sachet >9 years: 1 sachet ×2	68	Bowel preparation excellent in 59% (19/32) of children in the Pico-Salax group and 52.8% (19/36) of the magnesium citrate group	Majority (31/32 [96.9%]) of Pico-Salax group had no AEs. One patient had vomiting, cramping, and abdominal pain
Turner 2009	Pico-Salax: 2 doses, at 6 PM on the	83	More Pico-Salax patients (81%) were satisfied or	No clinically significant AEs except for 1 case of mild

	day before and 8 AM on day of procedure <6 years: ¼ sachet ×2 6-12 years: ½ sachet ×2 >12 years: 1 sachet ×2 Comparator: PEG-ELS		very satisfied compared with PEG-ELS (81% vs 48%; P = 0.001). No differences in bowel cleanout effectiveness.	dehydration in the Pico-Salax group. No clinically significant laboratory abnormalities.
DiNardo 2014	Picoprep: 2 doses, at 4 PM and 5 hours later on day before procedure <6 years: ¼ sachet ×2 6-12 years: ½ sachet ×2 >12 years: 1 sachet ×2 Comparator: 3 PEG-based products	299	No differences between Picoprep and the 3 PEG based products. Excellent or good cleanout in 90.3% Picoprep patients.	No SAEs in any group. Rates of tolerability, acceptability, and compliance were significantly higher in the Picoprep group.
Vejzovic 2016	Sodium picosulfate/magnesium citrate: 2 doses, at 8 AM and 6-8 hours later on day before procedure 10-18 years: 1 sachet × 2 Comparator: PEG-ELS	71	No significance difference between treatments based on Ottawa Bowel Preparation Quality Score.	Rates of acceptability and tolerability were significantly higher in the sodium picosulfate/magnesium citrate group than in the PEG-ELS group.

Source: Adapted from Applicant Submitted Clinical Overview p. 8, Table 4
*Prepopik is also known under the trade names Picolax, PicoSalax, Pico-Salax, and Picoprep
AEs = adverse events; PEG = polyethylene glycol; PEG-ELS = polyethylene glycol-electrolyte solution; SAEs = serious adverse events

Table 4. Clinical Studies of Prepopik* in Adults Under IND 124998 in Support of NDA 202535

	Primary Endpoint	Treatment Arms	N of Subjects Treated	N of Subjects Completing the Study	Proportion of Patients with Successful Colon Cleansing
FE2009-01 Split Dose	The proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent or Good according to the Aronchick Scale at Visit 3 during colonoscopy.	Picoprep	305/608	304 (99%)	256/304 (84%)
		HalfLytely	298/608	295 (100%)	221/297 (74%)
FE2009-02 Day Before	The proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent or Good according to the Aronchick Scale14 at Visit 3 during colonoscopy	Picoprep	296/598	287 (97%)	224/294 (83%)
		HalfLytely	302/598	295 (98%)	239/300 (80%)

Source: Adapted from Dr. Zana H. Marks, MD FDA Medical Officer primary clinical review of NDA 202535.

5.2. Review Strategy

The clinical review focused on Study 000103 in the Prepopik development program: A Randomized, Assessor-Blind, Multicenter, Dose-Ranging Study Comparing the Safety and Efficacy of Prepopik versus Polyethylene Glycol Preparation (Local Standard of Care) in Children Aged 9 Years to 16 Years," which compared the efficacy, safety, and tolerability of Prepopik to PEG. Review of the study was based primarily on this reviewer's independent analysis of the data sets provided by the Applicant, and secondarily on the Applicant's study reports. The tables and analyses presented in this report reflect the independent analysis of the reviewer except where otherwise noted. Narratives of patients with serious adverse events were reviewed; there were no deaths in the study. The Applicant's bibliography was reviewed when relevant.

Dr. Erica Lyons, medical officer, was the primary author for the review. Dr. Kathleen Donohue, cross-discipline team lead, and Dr. Lisa Soule, Associate Director, provided edits. Ling Lan, Ph.D., statistical reviewer, contributed Figures 2 & 3 and verified the results in Tables 12 & 14. George Kordzakhia, Ph.D., statistical team lead, provided edits. All five authors had access to the primary data. Drs. Lyons, Donohue & Soule concur with the conclusions in this review. Drs. Lan & Kordzakhia concur with the efficacy results in Section 6.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 000103

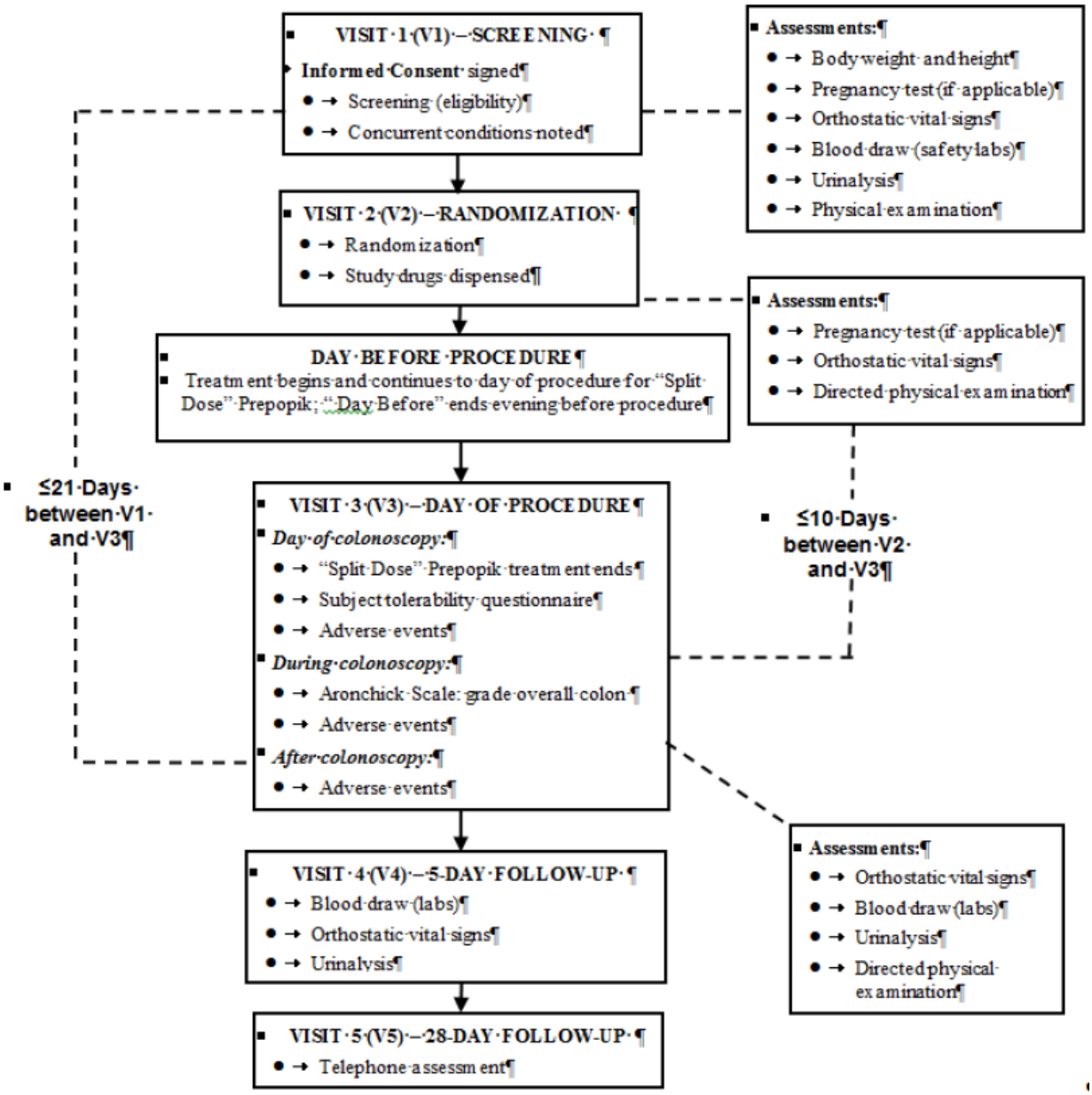
6.1.1. Study Design

Overview and Objective

The primary objective of Study 000103, "A Randomized, Assessor-Blind, Multicenter, Dose-Ranging Study Comparing the Safety and Efficacy of Prepopik versus Polyethylene Glycol Preparation (Local Standard of Care) in Children Aged 9 Years to 16 Years" was to determine whether Prepopik, at a dosage of either ½ sachet x 2 for those ages 9-12 years and/or 1 sachet x 2 for those ages 9-16 years had similar efficacy in cleansing the colon when compared to PEG in preparation for colonoscopy based on the Aronchick scale.[17]

[17] Aronchick CA, Lipshutz WH, Wright SH, DuFrayne F, Bergman G. Validation of an instrument to assess colon cleansing [abstract] Am J Gastroenterol. 1999; 94:2667.

Figure 1. Trial 000103 Study Design



Source: Applicant Submitted Clinical Study Report p. 17, Figure 1

Ferring Study 000103 was a randomized, assessor-blind, multicenter, dose-ranging study investigating the efficacy, safety, tolerability, and PK characteristics of Prepopik for colon cleansing in pediatric patients from 9 to 16 years of age. The study was conducted at nine investigative sites in the US.

Pertinent inclusion criteria

- Male or female ages 9-16 years scheduled to undergo an elective colonoscopy
- ≥ 3 spontaneous bowel movements per week for 1 month prior to the colonoscopy
- Females of childbearing potential with a negative pregnancy test at screening and randomization
- Willing, able, and competent to complete the procedure and study instructions

Pertinent exclusion criteria

- Acute surgical abdominal conditions
- Hospitalized for inflammatory bowel disease
- Prior colorectal surgery (excluding appendectomy, hemorrhoid surgery, or prior endoscopy)
- Colon disease (cancer, toxic megacolon, toxic colitis, idiopathic pseudo-obstruction, hypomotility syndrome, colon resection)
- Ascites
- Gastrointestinal disorder (active ulcer, outlet obstruction, retention, gastroparesis, ileus)
- Upper gastrointestinal surgery (gastric resection, banding, or bypass)
- Significant cardiovascular disease
- History of renal insufficiency with abnormal serum creatinine or potassium

Prohibited medications

- Lithium
- Laxatives < 24 hours prior to procedure
- Constipating drugs <2 days prior to procedure
- Antidiarrheals <72 hours prior to procedure
- Oral iron preparations <1 week prior to procedure

Investigational Product: Prepopik is a white crystalline powder for oral solution. Each sachet of Prepopik contains: sodium picosulfate 10 mg, magnesium oxide 3.5 g, and citric acid anhydrous 12 g. In water solution magnesium oxide and citric acid react to form magnesium citrate. Prepopik was supplied in boxes containing 2 foil sachets each.

Comparator: Oral PEG-based preparation was used in the study per standard of care.

Method of Randomization and Blinding:
At the visit preceding the colonoscopy, eligible subjects were randomized by age group. Subjects ages 9-12 years were randomized into 3 arms: Prepopik ½ sachet ×2, Prepopik 1 sachet ×2, or standard of care (i.e., PEG). Subjects aged 13 years to 16 years were randomized into 2 arms: Prepopik 1 sachet ×2 or local standard of care (i.e., PEG). Study treatments were allocated according to computer-generated randomization codes and were blinded to the

endoscopist and his/her assistant(s) performing the colonoscopy. An unblinded coordinator was responsible for distribution and accountability of the drug. One subject, Subject (b) (6) was randomized to the Prepopik ½ sachet ×2 arm, but received Prepopik 1 sachet ×2 and was therefore included in the Prepopik 1 ×2 sachet arm for the safety analysis set. A nondisclosure affidavit form was completed by the subjects/parents/guardians and the unblinded coordinator to further safeguard study blinding.

Table 5. Schedule of Assessments Study 000103

Visit	V1 Screening	V2 Randomization	V3 Colonoscopy	V4 Follow-up	V5 Telephone Follow-up
Day	≤ -42 days	≤ -14 days	T=0	5±2	28±5 days
Urine pregnancy test	X	X			
Laboratory (chemistry, hematology, coagulation, urinalysis)	X	X	X	X	
Physical examination	X		X		
Orthostatic vital signs (blood pressure, pulse)	X	X	X	X	
Adverse events		X	X	X	X
Pharmacokinetic (PK) assessment		X	X		
Perform colonoscopy/Aronchick scale			X		

Source: Adapted from Applicant Submitted Clinical Study Report p. 24, Table 2

Study Endpoints

The primary objective of the study was to describe the efficacy of Prepopik in children aged 9 years to 16 years for overall colon cleansing in preparation for colonoscopy based on the Aronchick scale as compared to oral polyethylene glycol (PEG)-based preparation/local standard of care. The primary efficacy endpoint was proportion of subjects whose cleansing was classified as a success, defined by "excellent" or "good" in the Aronchick scale.

Secondary endpoints were assed using a Tolerability and Satisfaction Questionnaire which assessed ease of use, taste, discomfort, fullness, night waking, nausea, and perceived burden of bathroom visits.

The Aronchick scale is universally accepted and designed to grade the adequacy of cleansing the entire colon using semi-quantitative descriptors. The scale has been validated for use in adult populations, and has been used in other pivotal trials including the approval in adults of

HalfLytely and Prepopik. It is also the scale against which other colon cleansing scoring systems, such as the Ottawa Bowel Preparation Scale, have been validated. The American Society for Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) Taskforce on Quality in Endoscopy suggests that every colonoscopy report should include an assessment of the quality of bowel preparation.[18]

Table 6. Aronchick Scale

Grade	Description
Excellent	>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization
Good	>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	<90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

Source: Adapted from Applicant submitted Clinical Study Report p. 25, Table 3

Statistical Analysis Plan

Approximately 75 subjects were to be enrolled. Eighty subjects underwent screening, of which 78 were enrolled. There were 3 analysis sets in this study: Intent-to-treat (ITT), Per-Protocol (PP), and Safety. All randomized subjects who received any study drug were included in 1 or more of the analysis data sets with no imputation for missing values.

1. Intent-to-treat Analysis Set (ITT, Full Analysis Set)
All randomized subjects who received any study treatment and produced efficacy assessment data (Aronchick) were included in the ITT analysis data set.

[18] Rex DK, Petrini JL, Baron TH, et al. Quality indicators for colonoscopy. Am J Gastroenterol. 2006; 101:873–85.

2. Per-Protocol (PP) Analysis Set
Subjects who had major protocol violations, including not taking study drug in the prescribed time intervals, were excluded from the PP analysis set. Subjects to be excluded from the PP analysis set were identified prior to breaking the study blind. Treatment assignment for summary and analysis was per randomization.

3. Safety Analysis Set
All subjects who received any study treatment were included in the Safety analysis data set. Treatment assignment for summary and analysis was based on actual treatment.

The primary endpoint analyses (the proportion of responders based on the Aronchick Scale) were performed on the All Randomized Subjects (ITT) analysis set.

All 78 subjects were included in the ITT analyses population, and 75 subjects were included in the safety population (due to 3 subjects in the comparator group receiving non-PEG standard care).

As there was no formal statistical testing pre-specified for the treatment comparison, no sample size calculation was conducted. Efficacy was assessed by constructing the 90% and 95% confidence intervals (CIs) of the proportions of the responder in each treatment arm and the difference in proportions of responders between each Prepopik group and the standard of care, by age group. The CIs were calculated based on the Clopper-Pearson method for each treatment arm and the exact method for the treatment difference, and multiplied by 100 to be presented as percentages. Of note, an additional measure of efficacy, the Ottawa Scale, which was a secondary endpoint in the adult studies of Prepopik under NDA 202535, was not included as an assessment in Study 000103.

The primary endpoint is consistent with the endpoint used in the adult studies for Prepopik under NDA 202535 (b) (4) .

Adult Study Design and Results
Trial design for the adult population studies was based on The Food and Drug Administration (FDA) “Guidance for Industry: Non-Inferiority Clinical Trials.” An anticipated responder rate of 85% was selected for analysis based on historical references. The analysis plan proposed that non-inferiority would be demonstrated if the 1-sided 97.5% CI for the treatment difference (Prepopik minus HalfLytely) was >-9% for the percentage of responders, and superiority would be demonstrated if the prespecified lower bound of the CI was >0%. For "split-dosing," the lower bound of the 1-sided 97.5% CI for the treatment difference was 3.4% in the ITT analysis set and 2.7% in the PP analysis set; thus, both NI and superiority of PICOPREP to HalfLytely was

demonstrated in both analysis sets. For "day-before dosing," the lower bound of the 1-sided 97.5% CI for the treatment difference was -2.9% in the ITT analysis set and -2.8% in the PP analysis set; thus, NI, but not superiority, of Prepopik to HalfLytely was demonstrated in both analysis sets.

Protocol Amendments

The original protocol February 4, 2013 was amended 4 times. Protocol amendments were primarily for administrative or clarification purposes. Of the amendments, only Amendment 4 (July 28, 2014) was implemented after initiation of patient enrollment. Seven of the 78 total subjects underwent colonoscopy and primary assessment prior to implementation of Amendment 4.

Amendment 1 (July 8, 2013) was not submitted to the sites or their respective IRBs, as the study had not yet started. It clarified that the second dose should be taken ≥ 6 hours after the first dose, revised the exclusion criteria allow for inclusion of diagnostic colonoscopy, clarified PK draw times and drug concentrations to be measured, added information on screening to the recruitment section, updated section 5 with comments from the Applicant Company's Investigational Medical Product (IMP) Department, removed detailed label information, added that deviations in storage temperatures must be reported and the IMP quarantined, added wording to the return and destruction of IMP section, and updated the electronic case report form section.

Amendment 2 (August 21, 2013) was not submitted to the sites or their respective IRBs, as the study had not yet started. It contained a changed planned start date, addition of the "Day Before" alternative dosing method, clarified that subjects should drink ≥5 glasses of clear liquids after the first dose and ≥ 3 glasses of clear liquids after the second dose, added a bicarbonate safety laboratory parameter, removed the word "global" from the adverse event section, and added to the confidential non-disclosure affidavit that subjects were not to disclose PK blood draws.

Amendment 3 (August 21, 2013) clarified blinding language to assessor and assessor's assistants, changed Visit 4 to a site visit with lab and vital signs, added PK clarification to the schedule of events, and specified lab samples would be processed locally.

Amendment 4 (July 28, 2014) eliminated the post-colonoscopy laboratory specimen collection and physical examination.

Reviewer Comment:
In the opinion of this medical reviewer, these changes are acceptable and do not raise concerns for data interpretation.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that the study was conducted in full accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (e.g., Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314;).

Financial Disclosure

For Study 000103, the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Patient Disposition

A total of 80 subjects underwent screening, of which 78 were randomized in this study. Forty-eight subjects aged 9 to 12 years were randomized into 3 arms: 16 to Prepopik ½ sachet ×2, 16 to Prepopik 1 sachet ×2, and 16 to local standard of care (PEG). Thirty subjects aged 13 to 16 years were randomized into 2 arms: 16 to Prepopik 1 sachet ×2 and 14 to PEG. A total of 75 subjects were included in the safety analysis set, as 3 subjects assigned to the PEG group received non-PEG-based standard of care. Subject (b) (6) was randomized to the Prepopik ½ sachet ×2 arm, but received Prepopik 1 sachet ×2 and was therefore included in the Prepopik 1 ×2 sachet arm for the safety analysis set.

All randomized subjects were included in the efficacy analysis (ITT set). For one subject, (b) (6), in the age 9-12 years Prepopik 1 sachet x 2 group, colonoscopy was started but not completed. This subject was included in the analysis, as an Aronchick score was provided. One subject each from the age 9-12 years Prepopik ½ sachet group and age 13-16 PEG group discontinued from the study due to "lost to follow up," but provided efficacy data.

Table 7. Subject Disposition by Age Group and Treatment

	N (%) of Subjects						
	Age 9-12 Years				Age 13-16 Years		
	Prepopik ½ Sachet ×2 (N = 16)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 16)	Total (N = 48)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 14)	Total (N = 30)
Randomized	16 (100)	16 (100)	16 (100)	48 (100)	16 (100)	14 (100)	30 (100)
Performed colonoscopy[d]	15 (94)	16 (100)	16 (100)	47 (98)	16 (100)	14 (100)	30 (100)
Per-Protocol Analysis Set[b]	12 (75)	15 (94)	15 (94)	42 (88)	14 (88)	12 (86)	26 (87)
Intention-to-Treat Analysis Set	16 (100)	16 (100)	16 (100)	48 (100)	16 (100)	14 (100)	30 (100)
Safety Analysis Set[b,c]	15 (94)	17 (106)	15 (94)	47 (98)	16 (100)	12 (86)	28 (93)
Pharmacokinetic Analysis Set	5 (31)	7 (44)	0	12 (25)	5 (31)	0	5 (17)
Completed colonoscopy [a]	15 (94)	15 (94)	16 (100)	46 (96)	16 (100)	14 (100)	30 (100)
Completed 5-day safety visit	15 (94)	15 (94)	15 (94)	45 (94)	16 (100)	11 (79)	27 (90)
Completed 1-month safety call	15 (94)	16 (100)	16 (100)	47 (98)	16 (100)	14 (100)	30 (100)
Complete d study	15 (94)	16 (100)	16 (100)	47 (98)	16 (100)	13 (93)	29 (97)
Discontinued from study/ (lost to follow up)	1 (6)	0	0	1 (2)	0	1 (7)	1 (3)

Source: Adapted from Applicant submitted Clinical Study Report p. 40 and p. 42, Tables 5-6
PEG = polyethylene glycol (standard of care)

a. For Subject (b) (6), colonoscopy was performed but not completed; however, Aronchick assessment for primary analysis was provided and was included in the efficacy analysis.
b. Subjects (b) (6), randomized to the PEG arm, were treated by the site's non-PEG-based standard of care and were excluded from the Per-Protocol and Safety analysis sets.
c. Subject (b) (6) was randomized to the Prepopik ½ sachet ×2 arm, but received Prepopik 1 sachet ×2 and was therefore included in the Prepopik 1 ×2 sachet arm for the Safety analysis set.
d. Subject (b) (6) randomized to Prepopik ½ sachet x 2 was initially dosed on March 25, 2015 but did not complete the second dose due to migraine, nausea, and vomiting. The subject was retreated using the same treatment regimen on March 31- April 1, 2015 and was included in the efficacy analysis; however, was not included in the Applicants disposition tables.

Reviewer comment:
Patient accountability was sufficiently maintained throughout the study and adequate efforts to prevent missing data from subjects lost to follow-up were undertaken. The cases in which subjects were lost to follow-up were balanced among treatment arms and occurred after the

primary assessment of efficacy; as such they do not impact the interpretability of the data.

Protocol Violations/Deviations

Of the 78 randomized subjects, 10 had protocol deviations that led to exclusion from the per protocol analysis set (six 9-12 year olds and four 13-16 year olds).

Prepopik ½ sachet, 9-12 years

- Subject (b) (6) did not complete dosing (this subject was retreated successfully at a follow-up visit after an initial attempt was stopped due to migraine, nausea, and vomiting)
- Two subjects received an incorrect dose of Prepopik.
    - One patient received too high a dose (1 sachet x 2 instead of ½ sachet x 2)
    - One patient received an unknown dose
- Study blind broken

Prepopik 1 sachet, 9-12 years

- Prohibited medication (ferrous sulfate was not stopped 1 week prior to the colonoscopy)

PEG 9-12 years

- Magnesium citrate instead of PEG for standard of care

Prepopik 1 sachet x 2, 13-16 years

- Subject did not complete dosing (abdominal pain, vomiting, hyperhidrosis)
- Incorrect timing of study preparation

PEG, 13-16 years

- Two subjects received magnesium citrate instead of PEG for standard of care

The most common protocol violations that did not lead to exclusion were assessment not completed per protocol and informed consent not obtained according to GCP.

Table 8. Protocol Violations

	N (%) of Deviation					
	Age 9-12 Years			Age 13-16 Years		
	Prepopik 1/2 SACHET	Prepopik 1 SACHET	PEG	Prepopik 1 SACHET	PEG	All
Analysis Category for Protocol Deviation						
Assessment not completed per protocol	13 (8)	20 (13)	25 (16)	26 (16)	34 (21)	118 (74)
Informed consent not obtained according to GCP	4 (3)	4 (3)	2 (1)	8 (5)	9 (6)	27 (17)
Subject prescribed Mag Citrate as SOC instead of PEG based colonoscopy prep	0	0	1 (1)	0	2 (1)	3 (2)
Minor deviation in dosing schedule	1 (1)	1 (1)	0	0	0	2 (1)
Subject did not complete IMP dosing	1 (1)	0	0	1 (1)	0	2 (1)
Assessment/Visit performed out of window	0	0	0	0	1 (1)	1 (1)
Dosing compliance	0	1 (1)	0	0	0	1 (1)
Drug Accountability	0	1 (1)	0	0	0	1 (1)
Liquid not consumed per protocol	1 (1)	0	0	0	0	1 (1)
Prohibited Medication	0	1 (1)	0	0	0	1 (1)
Significant deviation in dosing schedule	0	0	0	1 (1)	0	1 (1)
Study blind broken	1 (1)	0	0	0	0	1 (1)
Unknown Prepopik dosing	1 (1)	0	0	0	0	1 (1)
All	22 (14)	28 (18)	28 (18)	36 (23)	46 (29)	160 (100)

Source: Erica Lyons, MD FDA Medical Officer, ADDV.XPT

Reviewer comment:
With the exception of administration of nonstandard treatment in the PEG groups, protocol violations were balanced and do not present challenges to the assessment of efficacy.

Demographics

Selected demographic features for all randomized patients are shown inTable 9. **Study Demographics** Subject demographics and baseline characteristics were generally balanced among the treatment groups. The majority of subjects were female (68%), white (91%), and of non-Hispanic or non-Latino ethnicity (95%). The mean age was 12 years, with all subjects between 9 -16 years old.

Table 9. Study Demographics

	N (%) of Subjects							
	Age 9-12 Years				Age 13-16 Years			
	Prepopik ½ Sachet ×2 (N = 16)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 16)	Total (N = 48)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 14)	Total (N = 30)	Total (N = 78)
Sex								
F	11 (14)	12 (15)	8 (10)	31 (40)	11 (14)	11 (14)	22 (28)	53 (68)
M	5 (6)	4 (5)	8 (10)	17 (22)	5 (6)	3 (4)	8 (10)	25 (32)
Race								
White	15 (19)	16 (21)	11 (14)	42 (54)	15 (19)	14 (18)	29 (37)	71 (91)
Black or African American	0	0	5 (6)	5 (6)	1 (1)	0	1 (1)	6 (8)
Native Hawaiian or other Pacific Islander	1 (1)	0	0	1 (1)	0	0	0	1 (1)
Ethnicity								
Not Hispanic or Latino	16 (21)	14 (18)	15 (19)	45 (58)	15 (19)	14 (18)	29 (37)	74 (95)
Hispanic or Latino	0	2 (3)	1 (1)	3 (4)	1 (1)	0	1 (1)	4 (5)
AGE N	16	16	16	48	16	14	30	78
AGE Min	9	9	9	9	13	13	13	9
AGE Max	12	12	12	12	16	16	16	16
AGE Mean	10.8	10.5	10.4	10.5	15	14.9	15.0	12.2

Source: Erica Lyons, MD FDA Medical Officer, DM.XPT
Subject (b) (6) was randomized to the Prepopik ½ sachet ×2 arm, but received Prepopik 1 sachet ×2 and was therefore included in the Prepopik 1 ×2 sachet arm for the Safety analysis set.

Treatment Compliance and Concomitant Medications

Compliance was excellent with both dosages of Prepopik. Of all 48 subjects in the safety analysis set, 46 (96%) took both doses of Prepopik. All subjects took the first dose within the

protocol-specified time period. Of the 45 Prepopik subjects who took the second dose and had data on the timing of dosing available, 42 (88%) took the dose in the protocol-specified time period. Additional fluid consumption is required after dosing. Nearly all Prepopik subjects consumed the recommended liquids after dosing, 94% (45/48) were compliant after the first dose, and 90% (43/46) were compliant after the second dose.

Table 10. Dosing Compliance in Controlled Trials, Safety Population

	N (%) of Subjects				
	Age 9-12 Years		Age 13-16 Years		
	Prepopik ½ Sachet ×2 (N = 15)	Prepopik 1 Sachet ×2 (N = 17)	Prepopik 1 Sachet ×2 (N = 16)	Prepopik 1 Sachet ×2 (N = 33)	Any Prepopik (N = 48)
Dose regimen					
Split dose	3 (20)	5 (29)	5 (31)	10 (30)	13 (27)
Day before	12 (80)	12 (71)	11 (69)	23 (70)	35 (73)
Was dose taken?					
Dose 1					
Yes	15 (100)	17 (100)	16 (100)	33 (100)	48 (100)
No	0	0	0	0	0
Dose 2					
n	15	17	16	33	48
Yes	14 (93)	17 (100)	15 (94)	32 (97)	46 (96)
No	1 (7)	0	1 (6)	1 (3)	2 (4)
Within time period?[a]					
Dose 1					
Yes	15 (100)	17 (100)	16 (100)	33 (100)	48 (100)
No	0	0	0	0	0
Dose 2					
n	13[b]	17	15	32	45
Yes	11 (73)	16 (94)	15 (94)	31 (94)	42 (88)
No	2 (13.	1 (6)	0	1 (3)	3 (6)

Source: Adapted from Applicant Submitted Clinical Study Report p. 48, Table 9

a. Corresponding to the case report form question: 'Was first/second dosing of drug taken within the specified time period (± 30 min)?'

b. The question 'Was second dosing of drug taken within the specified time period (± 30 min)?' for Subject (b) (6) was not answered.

All subjects received at least one concomitant medication, the most common were those taken for sedation prior to colonoscopy. Table 11. Concomitant Medications Taken by ≥10% of All

Subjects by Age Group and Treatment Group (Safety Analysis Set) summarizes the most common concomitant medications for the study.

Table 11. Concomitant Medications Taken by ≥10% of All Subjects by Age Group and Treatment Group (Safety Analysis Set)

	N (%) of Subjects						
	Age 9 – 12 Years				Age 13-16 Years		
Therapeutic Class	Prepopik ½ Sachet ×2 (N = 15)	Prepopik 1 Sachet ×2 (N = 17)	PEG (N = 15)	Total (N = 47)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 12)	Total (N = 28)
Any concomitant medication	15 (100)	17 (100)	15 (100)	47 (100)	16 (100)	12 (100)	28 (100)
Anesthetics	14 (93)	17 (100)	13 (87)	44 (94)	16 (100)	12 (100)	28 (100)
Antiemetics/ antinauseants	13 (87)	15 (88)	13 (87)	41 (87)	11 (69)	9 (75)	20 (71)
Corticosteroids	8 (53)	7 (41)	7 (47)	22 (47)	6 (38)	7 (58)	13 (46)
Drugs for acid related disorders	6 (40)	7 (41)	6 (40)	19 (40)	8 (50)	7 (58)	15 (54)
Drugs for functional gastrointestinal disorders	4 (27)	6 (35)	7 (47)	17 (36)	6 (38)	4 (33)	10 (36)
Blood substitutes and perfusion solutions	4 (27)	6 (35)	6 (40)	16 (34)	5 (31)	4 (33)	9 (32)
Psycholeptics	2 (13)	6 (35)	6 (40)	14 (30)	5 (31)	5 (42)	10 (36)
Vitamins	6 (40)	3 (18)	5 (33)	14 (30)	3 (19)	5 (42)	8 (29)
Antidiarrheals, intestinal anti-inflammatory/ anti-infective agents	4 (27)	3 (18)	3 (20)	10 (21)	3 (19)	3 (25)	6 (21)
Antihistamines	4 (27)	5 (29)	2 (13)	11 (23)	2 (13)	2 (17)	4 (14)
Antibacterials	0	0	4 (27)	4 (9)	5 (31)	5 (42)	10 (36)
Analgesics	1 (7)	5 (29)	0	6 (13)	3 (19)	4 (33)	7 (25)
Psychoanaleptics	4 (27)	2 (12)	3 (20)	9 (19)	2 (13)	2 (17)	4 (14)
Anti-inflammatory	3 (20)	1 (6)	3 (20)	7 (15)	2 (13)	2 (17)	4 (14)
Antirheumatic products							
Drugs for constipation	3 (20)	3 (18)	2 (13)	8 (17)	1 (6)	2 (17)	3 (11)
Drugs for obstructive diseases	2 (13)	2 (12)	2 (13)	6 (13)	2 (13)	3 (25)	5 (18)
Immunosuppressants	2 (13)	2 (12)	3 (20)	7 (15)	1 (6)	2 (17)	3 (11)
Antianemic preparations	3 (20)	2 (12)	2 (13)	7 (15)	1 (6)	2 (17)	3 (11)
All other therapeutic	2 (13)	1 (6)	2 (13)	5 (11)	2 (13)	3 (25)	5 (18)

Source: Adapted from Applicant Submitted Clinical Study Report p. 46, Table 8
PEG = polyethylene glycol (standard of care)

Efficacy Results – Primary Endpoint

Responder rates of the primary endpoint were similar in the Prepopik 1 sachet x 2 and PEG treatment groups in both the 9 to 12-year age group (88% [90% CI: 66% – 98%] and 81% [90% CI: 58% - 95%], respectively) and the 13 to 16-year age group (81% [90% CI: 58% - 95%] and 86% [90% CI: 62% – 97%], respectively). A lower rate of response was observed for subjects ages 9-12 years who received Prepopik ½ sachet x 2 (50% [90% CI: 28% – 72%]).

There was one subject in whom the colonoscopy was not completed (Subject (b) (6)); however, an Aronchick scale was performed and included in the primary analysis. If this subject is treated as a non-responder, the responder rate in the 9-12-year cohort that received Prepopik 1 sachet x 2 decreased from 88% [90% CI: 66% – 98%] to 81% [90% CI: 58% – 95%].

Table 12. Aronchick Scale Results by Age Group and Treatment (ITT Analysis Set)

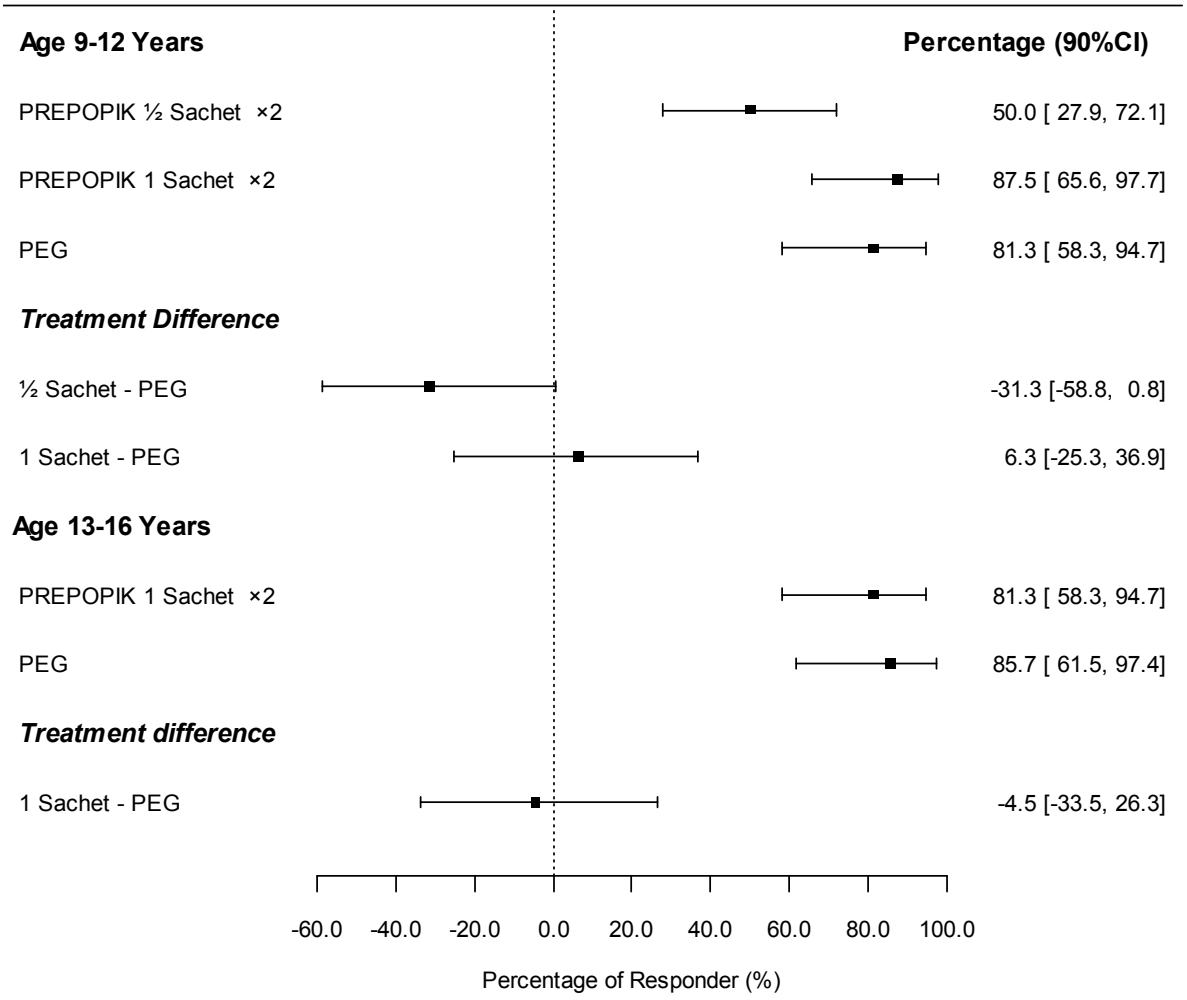
	N (%) of Subjects				
	Age 9-12 Years			Age 13-16 Years	
	Prepopik ½ Sachet ×2	Prepopik 1 Sachet ×2	PEG	Prepopik 1 Sachet ×2	PEG
ITT analysis set	N = 16	N = 16	N = 16	N = 16	N = 14
Responders, n (%)	8 (50)	14 (88)	13 (81)	13 (81)	12 (86)
95% CI for proportion	(25 – 75)	(62 – 98)	(54 – 96)	(54 – 96)	(57 – 98)
90% CI for proportion	(28 – 72)	(66 – 98)	(58 – 95)	(58 – 95)	(62 – 97)
Difference from PEG (%)	-31	6		-5	
95% CI for difference	(-63 – 6)	(-31 – 42)		(-39 – 32)	
90% CI for difference	(-59 – 1)	(-25 – 37)		(-34 – 26)	

Source: Applicant's Table 6.1 on Page 65 of the 000103-statistical-2.pdf, verified by Ling Lan, FDA Statistical Reviewer

CI = confidence interval; ITT = intention-to-treat; PEG = polyethylene glycol (standard of care)

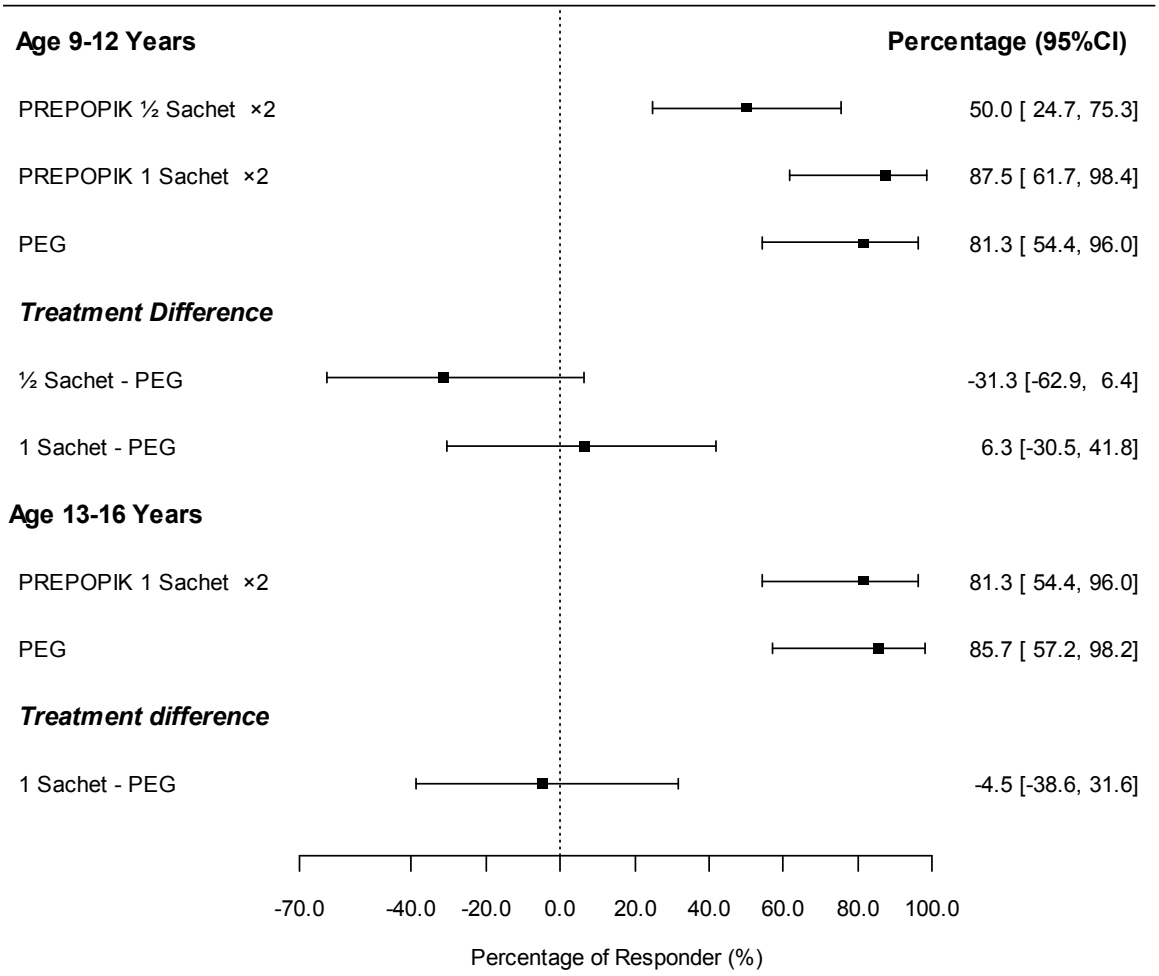
Note: Subjects (b) (6), randomized to the PEG arm, were treated by the site's non-PEG-based standard of care. The CIs for each treatment arm was calculated using the Clopper-Pearson method and the CI for the difference in proportions was based on exact methods.

Figure 2: Forest Plot for the Primary Endpoint: 90% CI



Source: Ling Lan, FDA Statistical Reviewer

Figure 3: Forest Plot for the Primary Endpoint: 95% CI



Source: Ling Lan, FDA Statistical Reviewer

Reviewer Comment:
During the initial protocol review for Study 000103, it was determined that a partial extrapolation of efficacy from the adult population was reasonable, given that adequate pediatric data was provided. In the opinion of this reviewer, the totality of the provided pediatric data from Study 000103, partial extrapolation from the efficacy data in adults, and the submitted literature citing the history of use of Prepopik products in children is adequate to support the approval of sNDA 202535 with a labeling change for Prepopik to include children 9 years of age and older at a dose of 1 sachet x 2.

Data Quality and Integrity – Reviewers' Assessment

The submission included a complete study report, proposed labeling, appropriate case report forms, and the relevant data sets. The study report was appropriately indexed and organized to allow review.

Review of the application does not raise any data integrity concerns.

Efficacy Results – Secondary and other relevant endpoints

Throughout both age groups, a greater percentage of subjects who received Prepopik rated ease of drinking as very easy or easy than those who received PEG (48% - 20%) and were never or rarely bothered about going to the washroom (44% - 13%). Fewer subjects who received Prepopik often or very often felt sick to their stomach compared to those who received PEG (17% - 40%).

Reviewer Comment:

(b) (4)

Table 13. Tolerability and Satisfaction Questionnaire Results by Age Group and Treatment (ITT Analysis Set)

	N (%) of Subjects				
	Age 9-12 Years			Age 13-16 Years	
	Prepopik ½ Sachet ×2 (N = 16)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 16)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 14)
Ease of drinking					
Very easy	4 (25)	2 (13)	1 (6)	2 (13)	0
Easy	5 (31)	4 (25)	1 (6)	6 (38)	4 (29)
Okay	3 (19)	4 (25)	4 (25)	7 (44)	5 (36)
Difficult	2 (13)	5 (31)	5 (31)	1 (6)	2 (14)
Very difficult	1 (6)	1 (6)	3 (19)	0	1 (7)
No rating	1 (6)	0	2 (13)	0	2 (14)
Taste					
Very well	1 (6)	0	1 (6)	1 (6)	1 (7)
Well	3 (19)	1 (6)	4 (25)	2 (13)	1 (7)
Okay	5 (31)	4 (25)	2 (13)	9 (56)	4 (29)

Bad	4 (25)	5 (31)	2 (13)	3 (19)	4 (29)
Very bad	2 (13)	6 (38)	5 (31)	1 (6)	2 (14)
No rating	1 (6)	0	2 (13)	0	2 (14)
How often tummy hurt					
Never	3 (19)	8 (50)	1 (6)	1 (6)	1 (7)
Rarely	1 (6)	1 (6)	1 (6)	3 (19)	4 (29)
Sometimes	5 (31)	6 (38)	6 (38)	9 (56)	3 (21)
Often	4 (25)	1 (6)	4 (25)	2 (13)	4 (29)
Very often	2 (13)	0	2 (13)	1 (6)	0
No rating	1 (6)	0	2 (13)	0	2 (14)
How often fell fullness in tummy					
Never	6 (38)	4 (25)	4 (25)	4 (25)	2 (14)
Rarely	3 (19)	4 (25)	4 (25)	3 (19)	2 (14)
Sometimes	2 (13)	5 (31)	1 (6)	4 (25)	5 (36)
Often	4 (25)	2 (13)	3 (19)	3 (19)	2 (14)
Very often	0	1 (6)	2 (13)	2 (13)	1 (7)
No rating	1 (6)	0	2 (13)	0	2 (14)
How often woke up last night					
Never	7 (44)	4 (25)	8 (50)	3 (19)	7 (50)
Rarely	3 (19)	8 (50)	3 (19)	4 (25)	1 (7)
Sometimes	4 (25)	1 (6)	0	4 (25)	2 (14)
Often	1 (6)	2 (13)	0	2 (13)	1 (7)
Very often	0	1 (6)	3 (19)	3 (19)	1 (7)
No rating	1 (6)	0	2 (13)	0	2 (14)
How often feel sick to stomach					
Never	4 (25)	7 (44)	3 (19)	4 (25)	1 (7)
Rarely	3 (19)	2 (13)	4 (25)	4 (25)	2 (14)
Sometimes	6 (38)	5 (31)	1 (6)	4 (25)	3 (21)
Often	1 (6)	1 (6)	2 (13)	3 (19)	3 (21)
Very often	1 (6)	1 (6)	4 (25)	1 (6)	3 (21)
No rating	1 (6)	0	2 (13)	0	2 (14)
How bothered were you about going to washroom					
Never	4 (25)	4 (25)	0	0	1 (7)

Rarely	5 (31)	3 (19)	2 (13)	5 (31)	1 (7)
Sometimes	2 (13)	2 (13)	1 (6)	4 (25)	2 (14)
Often	2 (13)	5 (31)	6 (38)	6 (38)	6 (43)
Very often	2 (13)	2 (13)	5 (31)	1 (6)	2 (14)
No rating	1 (6)	0	2 (13)	0	2 (14)

Source: Adapted from Applicants Clinical Study Report p. 52-53, Table 11
PEG = polyethylene glycol (standard of care); ITT = intention-to-treat

Dose/Dose Response

Among subjects 9-12 years of age, a decreased rate of response was seen with Prepopik ½ sachet x 2 versus Prepopik 1 sachet x 2 as described above.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable to this single study application.

7.1.1. Subpopulations

Given the significant concerns regarding the reliability of the efficacy data from the majority of subjects from Site 103, a subpopulation analysis was conducted for the primary efficacy endpoint excluding the 18 patients (23%) from Site 103 as shown below in Table 14.

Responder rates for the primary endpoint remained similar in the Prepopik 1 sachet x 2 and PEG treatment groups in both the 9 to 12-year age group (100% [90% CI: 79% – 100%] and 83% [90% CI: 56% - 97%], respectively) and the 13 to 16-year age group (83% [90% CI: 56% - 97%] and 90% [90% CI: 61% – 99%], respectively). A lower rate of response was observed for subjects ages 9-12 years who received Prepopik ½ sachet x 2 (46% [90% CI: 22% ‑ 71%]).

Table 14. Aronchick Scale Results by Age Group and Treatment (ITT Analysis Set Excluding Site 103)

	Age 9-12 Years			Age 13-16 Years	
	PREPOPIK ½ Sachet ×2 (N = 13)	PREPOPIK 1 Sachet ×2 (N = 13)	PEG (N = 12)	PREPOPIK 1 Sachet ×2 (N = 12)	PEG (N = 10)
ITT analysis set without Site 103					
Responders, n (%)	6 (46)	13 (100)	10 (83)	10 (83)	9 (90)
95% CI for proportion	(19, 75)	(75, 100)	(52, 98)	(52, 98)	(55, 100)
90% CI for proportion	(22, 71)	(79, 100)	(56, 97)	(56, 97)	(61, 99)
Difference from PEG (%)	-37	17		-7	
95% CI for difference	(-70, 2)	(-10, 48)		(-38, 29)	
90% CI for difference	(-66, -2)	(-5, 45)		(-33, 23)	

Source: Ling Lan, FDA Statistical Reviewer

CI = confidence interval; ITT = intention-to-treat; PEG = polyethylene glycol (standard of care)

Note: Subjects (b) (6), randomized to the PEG arm, were treated by the site's non-PEG-based standard of care

a. Responder = Excellent or Good on the Aronchick scale.
b. The CI was calculated using the Clopper-Pearson method.
c. The CI for the difference in proportions was based on exact methods.

Reviewer Comment:
The exclusion of Site 103 from the primary efficacy analysis did not have a substantial impact on the overall assessment of efficacy for Prepopik in Study 000103.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No differences are anticipated in how the drug was administered and used in the clinical trials versus its expected use in the postmarket setting that would be likely to affect efficacy.

7.2.2. Other Relevant Benefits

Ease of use and tolerability provide substantial benefit for administration of a bowel preparation. This is particularly pertinent when considering pediatric populations and may serve to enhance compliance with the regimen. (b) (4)

7.3. Integrated Assessment of Effectiveness

In summary, efficacy for Prepopik 1 sachet x 2 in pediatric subjects age 9 and older is supported by the data from Study 000103. Among subjects in the 9-12-year age group, the success rates were:

- Prepopik ½ sachet x 2 – 50%
- Prepopik 1 sachet x 2 – 88%
- PEG – 81%

Among subjects in the 13-16-year age group, the success rates were:

- Prepopik 1 sachet x 2 – 81%
- PEG – 86%

As noted in the initial review of NDA 202535, "Establishing a noninferiority margin based on a true treatment effect relative to placebo has been a recurrent issue discussed in FDA reviews of NDAs for bowel cleansing products, due to the lack of placebo controlled data (with any scoring system). Statistical reviewers have advocated setting a conservative NI margin in order to support a noninferiority claim, and if not met the clinical reviewers have examined the lower bound of the confidence interval for the observed success rate observed to determine if that rate exceeds what would be reasonably expected with a placebo in this setting."[19]

Although the limited sample size in Study 000103 did not permit for true assessment under a non-inferiority design, the above rationale applies and the supplied data is supportive of the effectiveness of Prepopik despite the uncertainty created by the wide confidence intervals; see Figure 2: Forest Plot for the Primary Endpoint: 90% CI and Figure 3: Forest Plot for the Primary Endpoint: 95% CI. Additionally, the selected comparator for the adult studies (HalfLytely) was less effective than the comparator for the pediatric studies (PEG). This difference in comparator success rates may contribute to the greater relative efficacy seen in adults treated with Prepopik and HalfLytely than in pediatric patients treated with Prepopik and PEG.

Given the similarity of percentage of responders across groups and partial extrapolation from efficacy in adult populations, it is reasonable to conclude that Prepopik at a dose of 1 sachet x 2 may be considered to have similar action to the comparator, PEG, in children 9 years of age and older.

It is important to note that the adult studies confirmed the enhanced efficacy of the "split-dose" treatment, thus it is classified as the preferred method in labeling. Although the limited study population did not allow for confirmation of that within Study 000103 (fewer than one-third of subjects randomized to Prepopik utilized the split-dose regimen), similar performance is

[19] NDA 202535 Division Director Review. Donna Griebel, MD. July 16, 2012.

expected. Finally, evidence from secondary endpoints for ease of use and tolerability are supportive of approval.

8. Review of Safety

8.1. Safety Review Approach

The safety review focuses on the population of patients who received at least one dose of study drug in Study 000103. Review was based primarily on this reviewer's independent analysis of the data sets provided by the Applicant, and secondarily on the Applicant's study report. The tables and analyses presented in this report reflect the independent analysis of the reviewer except where otherwise noted. Narratives of patients with serious adverse events were reviewed.

As a class, bowel preparations are known to cause fluid shifts that may result in clinical symptoms of dehydration, including dizziness, syncope/pre-syncope, and orthostatic changes. Of these, orthostatic changes emerged in the Prepopik program as a potential safety signal and are further discussed in sections 8.4.7 and 8.5.1.

Prepopik is a magnesium-containing product and caused expected increases in serum magnesium after administration. Additionally, significant shifts of serum glucose were seen in three subjects. These are further discussed in section 8.4.6.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Overall, 48 patients were exposed to one dose of Prepopik, and 46 patients were exposed to two doses. One subject, (b) (6), was randomized into the Prepopik 1/2 sachet x 2 group but received Prepopik 1 sachet x 2 and therefore was included in the Prepopik 1 sachet x 2 group for the safety database.

Table 15. Study Drug Exposure in Controlled Trials, Safety Population

	N (%) of Subjects				
	Age 9-12 Years		Age 13-16 Years		
	Prepopik ½ Sachet ×2 (N = 15)	Prepopik 1 Sachet ×2 (N = 17)	Prepopik 1 Sachet ×2 (N = 16)	Prepopik 1 Sachet ×2 (N = 33)	Any Prepopik (N = 48)
Dose was taken:					
Dose 1	15 (100)	17 (100)	16 (100)	33 (100)	48 (100)
Dose 2	14 (93)	17 (100)	15 (94)	32 (97)	46 (96)

Source: Adapted from Applicant Submitted Clinical Study Report p. 48, Table 9

8.2.2. Relevant characteristics of the safety population:

The most common medical history by system organ class were gastrointestinal disorders (98% any Prepopik and 100% PEG), infections/infestations (27% any Prepopik and 50% PEG), nervous system disorders (17% any Prepopik and 30% PEG), and surgical and medical procedures (21% any Prepopik and 23% PEG).

Of the gastrointestinal disorders, the most common were abdominal pain (63% any Prepopik and 60% PEG), diarrhea (27% any Prepopik and 27% PEG), constipation (19% any Prepopik and 30% PEG), Crohn's disease (25% any Prepopik and 20% PEG), and gastroesophageal reflux disease (23% any Prepopik and 23% PEG).

Table 16. Colonoscopy Results by Age Group and Treatment (ITT Analysis Set), provides a summary of colonoscopy results across the study population.

Table 16. Colonoscopy Results by Age Group and Treatment (ITT Analysis Set)

	N (%) of Subjects				
	Age 9-12 Years			Age 13-16 Years	
Overall Evaluation	Prepopik ½ Sachet ×2 (N = 16)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 16)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 14)
n [a]	15	16	16	16	14
Normal	10 (63)	14 (88)	12 (75)	9 (56)	11 (79)
Abnormal	5 (31)	2 (13)	4 (25)	7 (44)	3 (21)

Source: Adapted from Applicant Submitted Clinical Study Report p. 78, Table 29
PEG = polyethylene glycol (standard of care)
a. Subject (b) (6) did not have an overall evaluation of colonoscopy because she developed a migraine with vomiting and was discharged from the hospital to home.

8.2.3. Adequacy of the safety database:

The overall extent of exposure in the safety database with respect to number of patients and duration of treatment is adequate for review. However, as discussed below, a key piece of data regarding the safety signal of orthostatic change was not collected.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Incomplete orthostatic vital sign measurements were collected on a subject with a corresponding adverse event of lethargy. Absence of this data does not allow for exclusion of significant fluid shift and resultant orthostatic hypotension as a contributor to the adverse event.

Additionally, serum magnesium levels were not collected for the three patients evaluated at Site 108, including the above subject with lethargy. Absence of this data does not allow for exclusion of hypermagnesemia as a contributor to the adverse event.

8.3.2. Categorization of Adverse Events (AEs)

The Applicant's process for recording, coding, and categorizing AEs met minimum standards. The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols.[20]

Adverse events were defined as any untoward medical occurrence in a subject participating in a clinical trial and included:

- Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not considered to be caused by the study drug.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the study drug.
- Any laboratory abnormality, vital sign, or finding from physical examination assessed as clinically significant by the investigator (note: findings from assessments and examinations done during screening were not AEs, but were recorded as medical history).
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

[20] 21 CFR 312.32(a) and 314.80.

Serious adverse events were defined as death, life threatening, requiring or prolonging hospitalization, persistent or significant disability or incapacity, a congenital anomaly, or an important medical event requiring medical treatment to prevent one of these outcomes.

Adverse events were recorded from signature of the informed consent form through the end of the follow-up period, which was 28 days after the end-of-treatment visit. At each contact with the patient, the investigator asked the patient an open-ended question such as, "How have you been feeling since your last visit?". Severity was assessed using a 3-point rating scale:

- Mild: Awareness of signs or symptoms but no disruption of usual activity.
- Moderate: Event sufficient to affect usual activity (disturbing).
- Severe: Inability to work or perform usual activities (unacceptable).

Causality of the event to study drug was categorized as reasonable possibility or no reasonable possibility based on timing, biological plausibility, and presence of comorbid illnesses. Treatment-Emergent Adverse Events were defined as any AE that began during the treatment period or was a worsening of a pre-existing medical condition.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), versions 16.1 - 20.0. Verbatim terms were included in the file. The Applicant's translation of verbatim terms to preferred terms and subsequent categorization of preferred terms was adequate.

Adverse drug reactions (ADRs) were defined as AEs evaluated by the investigator as being probably or possibly causally related to treatment with Prepopik.

8.3.3. Routine Clinical Tests

Routine clinical testing was acceptable. Complete blood counts with differentials, coagulation panels, full chemistry panel including calculated creatinine clearance and serum magnesium, and urinalysis were collected during visits for screening, colonoscopy, and initial follow-up. Urine pregnancy tests were performed for female subjects of childbearing potential at visits for screening and randomization. See Table 5. Schedule of Assessments Study 000103**,** for schedules of procedures and assessments. Laboratory specimens were analyzed at the study site's local laboratory using appropriately validated methods. Out-of-range values were described in local reference ranges and were assessed by investigators as either clinically significant or not clinically significant.

8.4. Safety Results

8.4.1. Deaths

There were no deaths.

8.4.2. Serious Adverse Events

One Serious Adverse Event (SAE) occurred before initiating study drug. Subject (b) (6) had an abnormal hepatobiliary scan noted 5 days before the first dose of Prepopik that subsequently resulted in a cholecystectomy. There were no treatment-emergent SAEs.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No subject experienced a TEAE that led to discontinuation from the study. Two subjects did not receive the second dose of Prepopik due to TEAEs. Subject (b) (6) (Prepopik ½ sachet x 2 group) experienced migraine, nausea, and vomiting that led to interruption of the study drug and postponing of the colonoscopy. These events were considered by the investigator to be moderate in severity and related to the study drug. This subject was retreated at a later date and completed the study through the 28-day follow-up. Subject (b) (6) (Prepopik 1 sachet x 2 group) experienced abdominal pain, vomiting, and hyperhidrosis that led to interruption of the study drug. These events were considered moderate (vomiting and hyperhidrosis) to severe (abdominal pain) and were considered by the investigator to be related to the study drug. This patient did complete the colonoscopy and 28-day follow-up despite the incomplete treatment.

8.4.4. Significant Adverse Event

Although described as clinically insignificant by the Applicant, there was a notable increase in subjects with orthostatic changes between Prepopik and PEG groups with the greatest percent of subjects affected in the 9 – 12-year old age group. Notably, these changes occurred at similar rates in both the ½ sachet x 2 and 1 sachet x 2 treatment groups, suggesting dose-independence.

Table 17. Subjects with Orthostatic Changes of Interest for Vital Sign Values by Treatment

	N (%) of Subjects		
	Prepopik 1 SACHET x 2 (N = 33)	**ANY Prepopik (N = 48)**	**PEG (N = 27)**
Systolic blood pressure (mmHg) Decrease ≥ 20	2 (6)	2 (6)	1 (4)
Diastolic blood pressure (mmHg) Decrease ≥ 10	3 (9)	3 (6)	0
Pulse rate (beats/min)			
Increase ≥ 30	6 (18)	9 (19)	2 (7)
With decrease in systolic blood pressure	2 (6)	4 (8)	2 (7)
With decrease in diastolic blood pressure	3 (9)	5 (10)	0

Source: Adapted from Applicant submitted Clinical Study Report p. 77, Table 27
PEG = polyethylene glycol (standard of care)

Table 18. Subjects with Orthostatic Changes of Interest for Vital Sign Values by Age Group and Treatment

	N (%) of Subjects				
	Age 9-12 Years			Age 13-16 Years	
	Prepopik 1/2 SACHET x 2 (N = 15)	Prepopik 1 SACHET X 2 (N = 17)	PEG (N = 15)	Prepopik 1 SACHET X 2 (N = 16)	PEG (N = 12)
Systolic blood pressure (mmHg) Decrease ≥ 20	0	1 (6)	0	1 (6)	1 (8)
Diastolic blood pressure (mmHg) Decrease ≥ 10	0	2 (12)	0	1 (6)	0
Pulse rate (beats/min)					
Increase ≥ 30	3 (20)	4 (24)	1 (7)	2 (13)	1 (8)
With decrease in systolic blood pressure	2 (13)	1 (6)	1 (7)	1 (6)	1 (8)
With decrease in diastolic blood pressure	2 (13)	2 (12)	0	1 (6)	0

Source: Adapted from Applicant submitted Clinical Study Report p. 77, Table 28
PEG = polyethylene glycol (standard of care)

Though none of the subjects with a positive assessment for orthostasis was noted to have a AE that was considered possibly related, Subject (b) (6) with listed AE of lethargy did not have full orthostatic vital signs recorded at the colonoscopy visit (only supine measurements were performed). This protocol deviation was considered minor by the Applicant and did not result in subject exclusion from the per protocol analyses. Of note, this subject also had concurrent AEs of abdominal pain, hematochezia, hand-foot-and mouth disease, mouth ulceration, flatulence, and worsening of skin infection, and the episode of lethargy did not coincide with a significant decrease in serum sodium, (baseline 139 mmol/L, colonoscopy 138 mmol/L, end of study 138 mmol/L, normal range 138-145).

Reviewer Comment:
It is not possible to determine whether orthostatic changes contributed to the AE of lethargy for Subject (b) (6) *without complete vital signs at time of colonoscopy available for review. Though the subject was within the lower age cohort, which theoretically increased the risk for orthostasis, he had a concurrent illness at the time of evaluation, which may have contributed to his symptoms. His serum sodium did not significantly decrease from baseline to indicate a significant fluid shift that would cause orthostasis. High levels of serum magnesium can also*

cause lethargy; however, as noted below no serum magnesium values were recorded for subjects at this site. Causality for the AE of lethargy is not able to be established. Additionally, a decrease in the incidence of orthostatic was not seen in those subjects who received the lower ½ sachet x 2 dose of Prepopik.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The percentages of subjects with any TEAE (48% and 63%) or any adverse drug reaction (ADR) (10% and 19%) were lower in the any Prepopik group than in the PEG treatment group. Subgroup analysis by age revealed similar results, with the exception of a higher incidence of any TEAE (53% and 40%) between subjects age 9 – 12 years who received Prepopik ½ sachet x 2 and those who received PEG. Notably, there was a greater incidence of TEAEs and ADRs among both treatment groups for the age 13 – 16 group as compared to the age 9 – 12-year cohort.

Table 19. Overall Summary of Treatment-Emergent Adverse Events by Age Group and Treatment (Safety Analysis Set)

	N (%) of Subjects						
	Age 9-12 Years			Age 13-16 Years			
Category	Prepopik ½ Sachet ×2 (N = 15)	Prepopik 1 Sachet ×2 (N = 17)	PEG (N = 15)	Prepopik 1 Sachet ×2 (N = 16)	PEG (N = 12)	Any Prepopik (N = 48)	Any PEG (N = 27)
Any TEAE	8 (53)	5 (29)	6 (40)	10 (63)	11 (92)	23 (48)	17 (63)
Deaths	0	0	0	0	0	0	0
Serious TEAEs	0	0	0	0	0	0	0
TEAEs leading to discontinuation	0	0	0	0	0	0	0
Severe AEs	0	0	0	1 (6)	0	1 (2)	0
Any ADR	1 (7)	0	1 (7)	4 (25)	4 (33)	5 (10)	5 (19)
Serious ADRs	0	0	0	0	0	0	0

Source: Adapted from Applicant Submitted Clinical Study Report p. 57, Table 13 and p. 58, Table 14
ADR = adverse drug reaction; PEG = polyethylene glycol (standard of care); TEAE = treatment-emergent adverse event

As expected, the majority of adverse events seen were gastrointestinal disorders. Table 20 lists common AEs (≥2%) for the safety population of 75 subjects. Of the 78 enrolled subjects, three subjects in the comparator group did not receive PEG and as such were not included in the safety population.

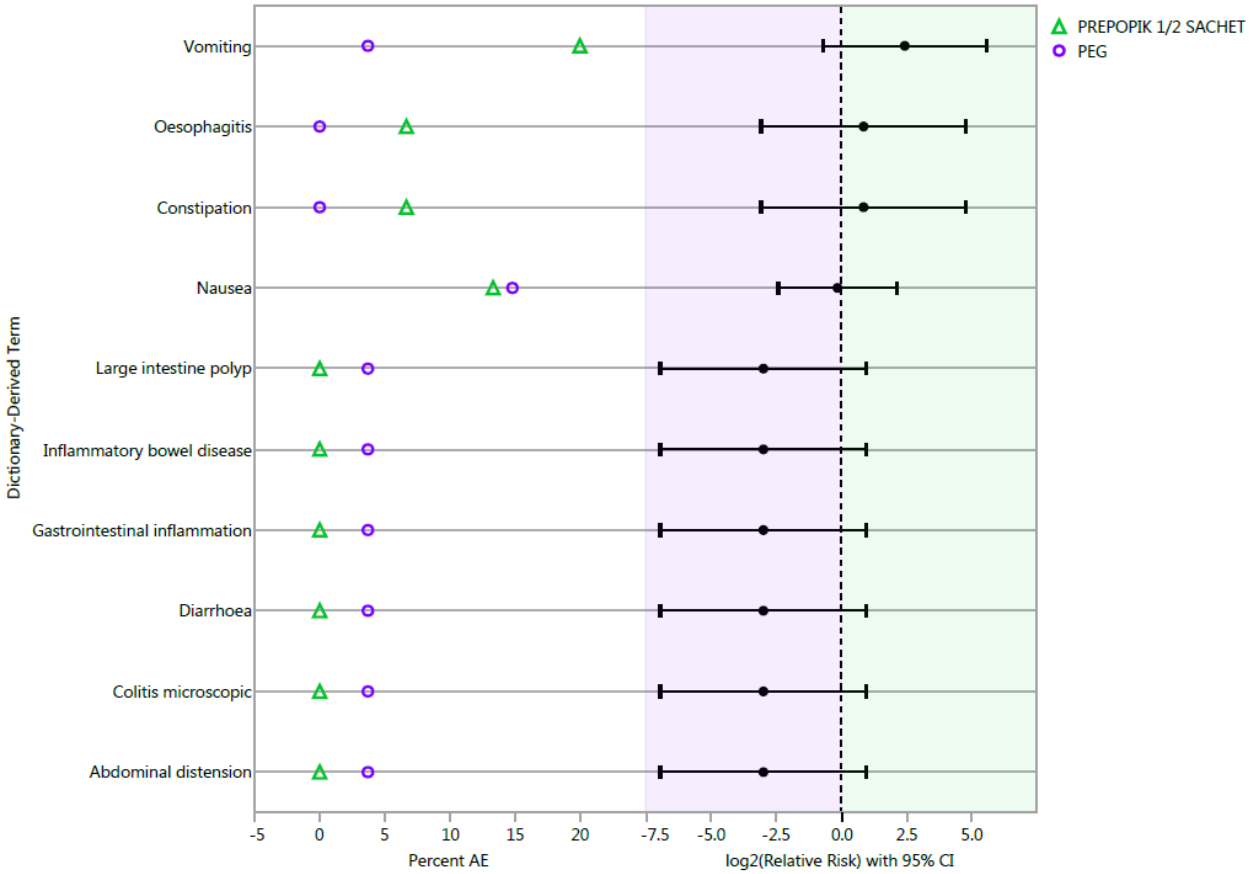
Table 20. Adverse Events with ≥ 2% Occurrence: All Event Types for All Subjects Chosen

	N (%) of Subjects			
	Prepopik 1/2 SACHET	**Prepopik 1 SACHET**	**PEG**	**Total**
Total	N=15	N=33	N=27	N=75
Gastrointestinal disorders	6 (40)	6 (18)	8 (30)	20 (27)
Abdominal pain		2 (6)		2 (3)
Gastrointestinal inflammation		1 (3)	1 (4)	2 (3)
Hematochezia		2 (6)		2 (3)
Large intestine polyp		1 (3)	1 (4)	2 (3)
Crohn's disease	1 (7)		1 (4)	2 (3)
Nausea	2 (13)	2 (6)	4 (15)	8 (11)
Esophagitis	1 (7)	1 (3)		2 (2)
Vomiting	3 (20)	2 (6)	1 (4)	6 (8)
General disorders and administration site conditions	1 (7)		1 (4)	2 (3)
Pyrexia	1 (7)		1 (4)	2 (3)
Investigations		2 (6)	3 (11)	5 (7)
White blood cell count increased		1 (3)	1 (4)	2 (3)
White blood cells urine positive		1 (3)	2 (7)	3 (4)
Nervous system disorders	1 (7)		1 (4)	2 (3)
Headache	1 (7)		1 (4)	2 (3)
Respiratory, thoracic and mediastinal disorders		1 (3)	4 (15)	5 (7)
Respiratory disorder			2 (7)	2 (3)
Oropharyngeal pain		1 (3)	2 (7)	3 (4)

Source: Erica Lyons, MD FDA Medical Officer, ADAE.XPT

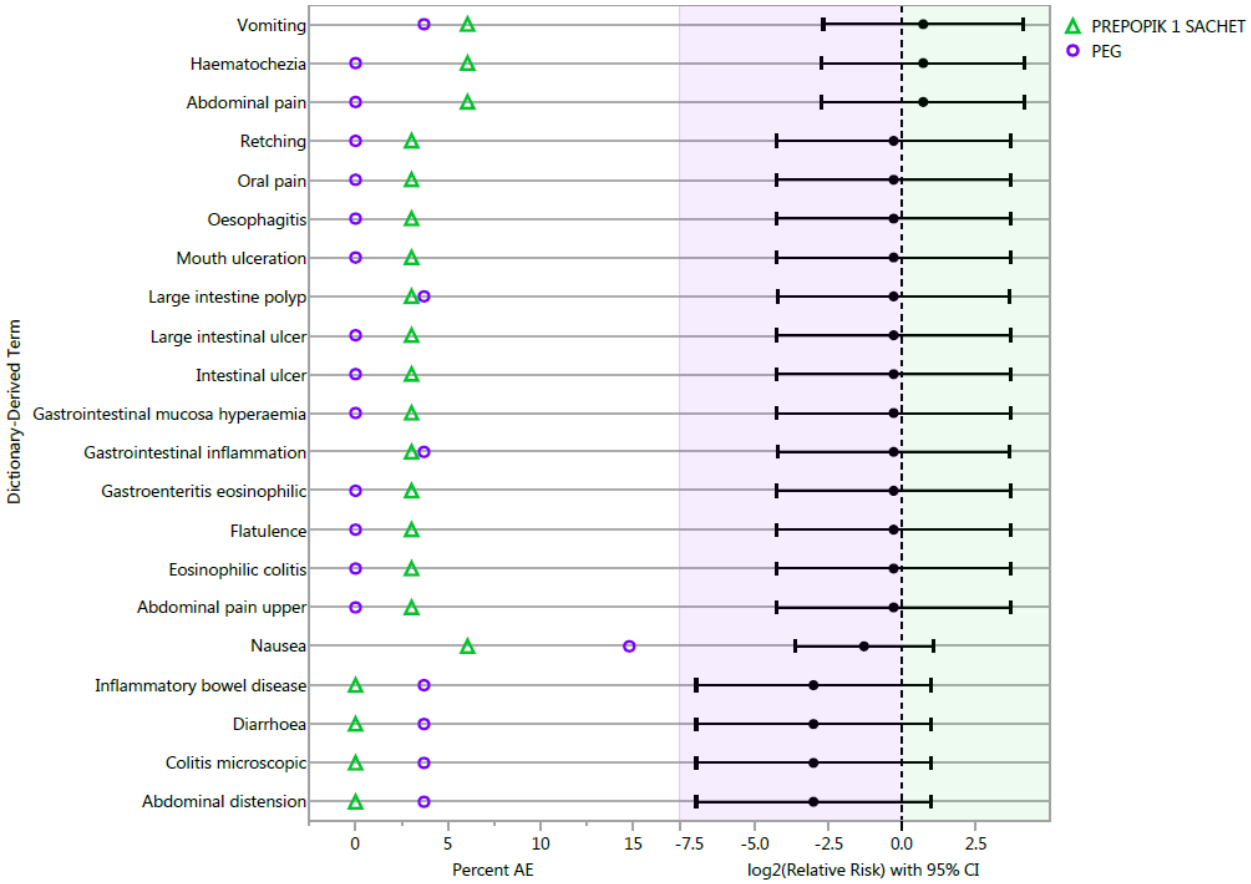
Of the gastrointestinal adverse events, vomiting was more prevalent in both Prepopik groups when compared to PEG as shown in Figure 4 and Figure 5.

Figure 4. Relative Risk of Gastrointestinal AEs, Prepopik 1/2 Sachet x 2 versus PEG



Source: Erica Lyons, MD FDA Medical Officer, ADAE.XPT

Figure 5. Relative Risk of Gastrointestinal AEs, Prepopik 1 Sachet x 2 versus PEG



Source: Erica Lyons, MD FDA Medical Officer, ADAE.XPT

Reviewer Comment:
Of the common AEs, although the relative risk for vomiting was higher in the Prepopik groups, the risk of nausea was equivalent or less. Both are known AEs of bowel preparations, and do not raise concern for a new safety signal. The increased frequency of reported adverse reactions in the 13 – 16-year-old age group as compared to the 9 – 12-year group may be due to variability in reporting by developmental stage.

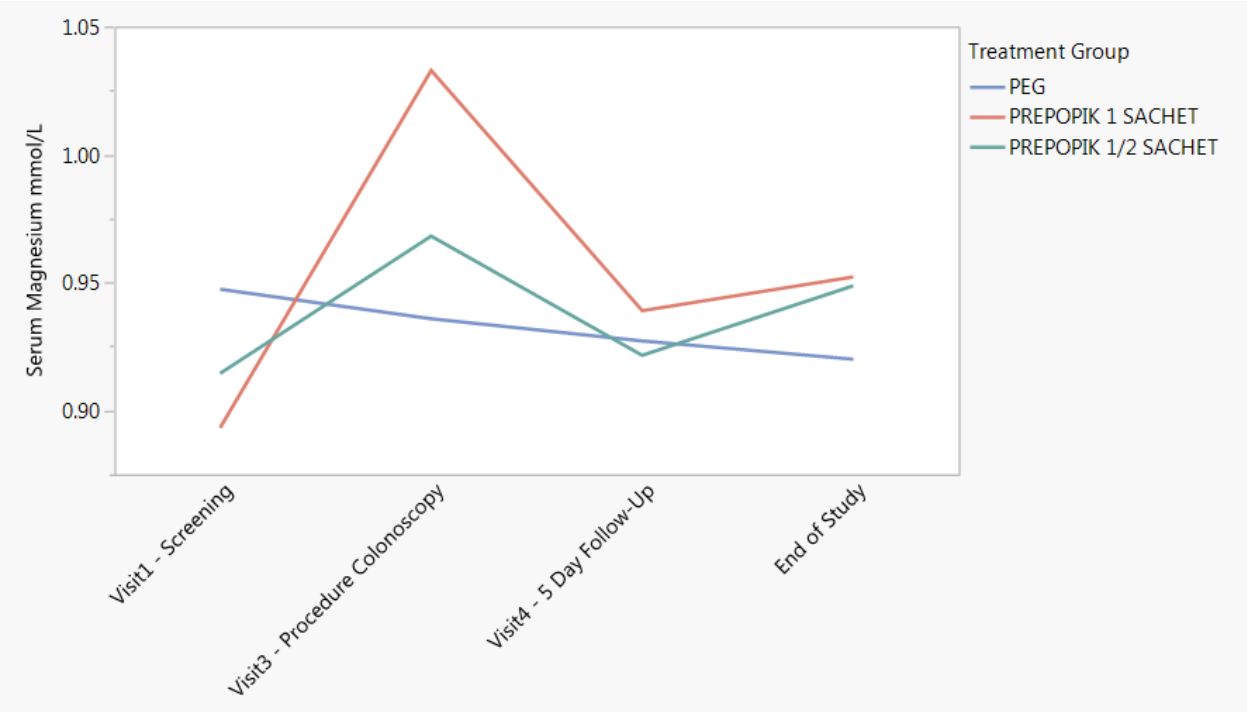
8.4.6. Laboratory Findings

A review of laboratory results from Study 000103 was notable for expected increases in serum magnesium consistent with ingestion of the magnesium citrate component in subjects who received Prepopik. Of these increases from Visit 1 – Screening to Visit 3 – Colonoscopy, by individual patient, there were nine transitions from normal to high (three – Prepopik ½ sachet x 2, six – Prepopik 1 sachet x 2) and one transition from low to high (Prepopik 1 sachet x 2).

Though evaluated at various local laboratories with individual specific reference ranges, it is important to note that none of the recorded values exceeded the standard definition of hypermagnesemia at 1.1 mmol/L and were trending towards normalization at the end of the study. Apart from these findings, there were no clinically significant electrolyte laboratory abnormalities observed in a review of mean change from baseline and shift plot and table analyses.

As noted above, serum magnesium levels were not recorded for subjects at Site 108, which included a subject with the AE of lethargy.

Figure 6. Mean Serum Magnesium by Study Visit and Treatment Group, (Safety Population)



Source: Erica Lyons, MD FDA Medical Officer, ADLB.XPT

Reviewer Comment:
Caution should be used when administering magnesium-containing compounds to subjects with impaired renal function.[21] This is addressed in the current Prepopik label under contraindications and warnings and precautions.

It is unfortunate that no serum magnesium levels were collected for the three subjects at Site

[21] Musso CG Magnesium metabolism in health and disease. Int Urol Nephrol 2009; 41:357-62.

108. As discussed in Section 8.4.4. above, Subject (b) (6) *had the AE of lethargy. Though alternate etiologies have already been discussed in this review, high magnesium as an etiology cannot be excluded.*

Three subjects experienced markedly abnormal glucose values ((2.2-2.6 mmol/L = 40-47 mg/dL) during the study. Of these two subjects received Prepopik 1 sachet x 2 (one in the 9-12-year cohort and one in the 13-16 cohort) and one subject received PEG (13-16-year cohort). This is consistent with a known class effect in pediatric patients of ingestion of a noncaloric product during a time of peri-procedure fasting. The abnormal values occurred at the 5 Day follow-up visit for two subjects (PEG and Prepopik 1 sachet x 2) and at the colonoscopy visit for the remaining subject (Prepopik 1 sachet x 2). There were no adverse events associated with the abnormal glucose values.

Reviewer Comment:
Although indicated for an expanded age group including younger patients with presumably greater risk for hypoglycemia, the current labeling for Nulytely includes discussion of the potential for hypoglycemia specifically in children younger than 2 in the Pediatric Use section. Given the lack of available pediatric bowel preparations, the episodes of hypoglycemia seen in this trial, and the potential for off-label use in younger age groups; it is appropriate to include a similar description of the potential for hypoglycemia within the Pediatric Use section in the Prepopik labeling.

8.4.7. **Vital Signs**

Vital signs were measured at baseline/screening, visit for colonoscopy, and initial follow-up visit. One subject in the Prepopik 1 sachet x 2 group had a TEAE related to a vital sign abnormality (hypertension on the day of the colonoscopy, assessed to be mild in severity and not related to study drug). Though a greater percentage of subjects in the Prepopik 1 sachet x 2 and any Prepopik treatment groups, compared to those treated with PEG, had shifts to high supine systolic blood pressure (9%, 6%, and 0%), high standing diastolic blood pressure (3%, 6%, and 0%), and high standing pulse rate (18%, 19%, and 11%); there was a notable increase in subjects with orthostatic changes between Prepopik and PEG groups with the greatest percent of subjects affected in the 9 – 12 year old age group as described above in section 8.4.4.

8.4.8. **Electrocardiograms (ECGs)**

No ECGs were included in this submission.

8.4.9. Immunogenicity

Immunogenicity was not anticipated and was not assessed in this submission. The adverse event profile of Prepopik does not suggest an immunogenic effect.

8.5. Analysis of Submission-Specific Safety Issues

A review of safety information from Study 000103 and postmarketing use of Prepopik in adults has not prompted any submission-specific safety concerns. The adverse events described are consistent with those previously described and labeled in other approved osmotic bowel cleansing agents.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Studies including Ames assay, a mouse lymphoma assay, and a micronucleus assay in mice were conducted as part of the initial NDA for Prepopik and did not show mutagenic potential. Due to the very short treatment duration, no long-term studies in animals have been performed to evaluation the carcinogenic potential of Prepopik.

8.8.2. Human Reproduction and Pregnancy

Per Division of Pediatric and Maternal Health review:[22]
"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.

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.

[22] Dr. Catherine Roca, Division of Pediatric and Maternal Health Review. sNDA 202535, April 20, 2018.

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.[23] 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.

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."

Updates to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Prepopik labeling were recommended to be consistent with the Pregnancy and Lactation Labeling Rule.

8.8.3. Pediatrics and Assessment of Effects on Growth

Study 000103 is the first of three PMR studies (1902-1, 1902-2, and 1902-3) intended to fulfill the PREA requirements for Prepopik. Additional studies for subjects 2 – 9 years of age and 12 months - 2 years of age are pending. A waiver for assessment in children less than 12 months of age has been granted. Study 000103 was submitted to fulfill PMR 1902-1. The current efficacy supplement was presented at the Pediatric Research Committee (PeRC) on August 1, 2018, and PeRC concurred with the Division that PMR 1902-1 is considered fulfilled.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose were reported in the Prepopik clinical program. It is likely that overdosage would lead to profuse diarrhea and treatment for overdose would consist of general supportive measures and maintenance of fluid intake. A patient who has taken an overdose should be monitored carefully and treated symptomatically for complications.

There is no known potential for abuse with Prepopik. Withdrawal and rebound are not applicable.

[23] 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.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The following evaluations were done to assess the post-marketing safety experience with the active drug combination (sodium picosulfate magnesium citrate): review of FDA Adverse Events Reporting System (FAERS) database, clinical safety updates submitted to NDA 202535, and published literature.

Review of FAERS Database:
During the review of Clenpiq (sodium picosulfate magnesium citrate pre-mixed solution NDA 209589, Ferring Pharmaceuticals, approved November 28, 2017), OSE/DPV I reviewers completed a search of the FAERS database for Prepopik powder for oral solution. The results of this search are detailed in the pharmacovigilance memorandum dated April 20, 2017 by Dr. Lisa Harinstein.[24]

This review identified several cases of "altered consciousness" as a frequent precursor symptom to hyponatremia. Further examination of these identified cases suggested a temporal association of neurologic events during or following the intake of the drug product. Therefore, the term "altered consciousness" and related terms (confusion, delirium, loss of consciousness) were included in the Patient Counseling section of the PI (17.0) and the Medication Guide.

The reviewers also concluded that while hyponatremia, electrolyte imbalance, and seizures/convulsions continue to be reported post-marketing, there was no new information pertaining to specific risk factors or subgroups of patients that would warrant an update to labeling. There was no new information identified with regard to ischemic colitis or ulcerative colitis. No risk evaluation and/or mitigation strategy was recommended due to this finding.[25]

Review of safety updates submitted to NDA 202535:
Safety updates were submitted to NDA 202535 on 01/31/2017 and 05/26/2017. The updates include information on the world-wide regulatory status of Ferring products containing the proposed active drug combination (SPMC), ongoing or completed clinical trials with the SPMC, foreign approvals, new clinical safety data, postmarketing safety data, and clinical safety data from published biomedical literature.

The Applicant noted that there were no significant changes to the safety profile of the active moieties in Prepopik within the presented data. The following is a summary of relevant information from the Applicant's safety updates:

[24] Pharmacovigilance memo NDA 209589. April 20, 2017. Drs. Lisa Harinstein, Eileen Wu, and Monica Munoz.

[25] Dr. Preeti Venkataraman, CDTL Review Clenpiq. November 20, 2017.

- Regulatory status: There have been no regulatory agency actions taken for safety reasons in any country, such as rejection or revoking of licensing applications, modifications to drug dose, target population or indication, suspensions of active clinical trials or issuance of "Dear Healthcare Provider" or equivalent notifications for safety issues. As of March 31, 2017, Ferring SPMC powder for oral solution is approved in 77 countries.

- Recently completed or ongoing clinical trials: AEs reported in recent trials with the SPMC appeared to be within the known safety risk profile of the active drug combination. The most commonly reported type of adverse reactions in the cumulative safety data were GI-related, including vomiting, diarrhea, nausea, and abdominal pain. Post-marketing data revealed no significant change to the safety profile.

Review of published literature:
A review of the published literature suggests that, in general, the adverse events reported in recent clinical trials correspond to the known safety profile of Prepopik. Few published case reports and abstracts noted electrolyte abnormalities, and neurological symptoms, with or without seizures in some patients who received SPMC. Risk factors included advanced age, underlying diseases, concomitant medication use, as well as lack of adherence to dosing instructions that may have led to either dehydration or acute fluid overload.[26,27,28,29,30]

8.9.2. Expectations on Safety in the Postmarket Setting

The majority of AEs identified during post-marketing review of the FAERS database and the medical literature for Prepopik and/or other SPMC formulations are within the known risk profile of the drug combination. The label for Prepopik should reflect the inclusion of "altered consciousness" and related terms as identified during the review of Clenpiq.

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[26] Bowel prep hyponatremia– a state of acute water intoxication facilitated by low dietary solute intake: case report and literature review. Windpessl et al, BMC Nephrology (2017) 18: 54.

[27] Sa1066- Comparison of Efficacy, Tolerability and Safety of Polyethylene Glycol Versus Sodium Picosulfate for Colon Cleansing in Elderly Patient; Kim et al, Gastrointestinal Endoscopy Volume 83, N0. 5S: 2016.

[28] Acute Hyponatremia With Seizure and Mental Change After Oral Sodium Picosulfate/Magnesium Citrate Bowel Preparation. Cho et al, Annals of Coloproctology, 30(6): 290-293.

[29] Metabolic Effects of Sodium Picosulfate/Magnesium Citrate (Citrafleet®) Bowel Preparation in Healthy Adults: Evaluation of Four Dosing Regimens, Balaban et al, Gastrointestinal Endoscopy, Volume 77, No. 5s: 2013.

[30] Dr. Sandhya Apparaju, Clinical Review Clenpiq. October 25, 2017.

8.9.3. Additional Safety Issues from Other Disciplines

8.10. Integrated Assessment of Safety

The safety database included n=33 patients treated with Prepopik at the to-be-marketed dose of 1 sachet x 2, n=15 patients treated with Prepopik at ½ sachet x 2, and n=27 patients randomized to the active comparator PEG. There were no deaths in the program and one serious adverse event, which occurred prior to treatment with Prepopik. The most common adverse events of nausea and vomiting were distributed equitably among Prepopik and comparator arms and are expected adverse class effects of bowel preparations.

Of note, there was an increase in subjects with orthostatic changes between Prepopik and PEG groups with the greatest percent of subjects affected in the 9 – 12-year-old age cohort. Missing data as described in Section 8.4.4. did not allow for a complete exclusion of clinical symptoms associated with this finding.

Review of laboratory results from Study 000103 demonstrated expected increases in serum magnesium consistent with ingestion of the magnesium citrate component in subjects who received Prepopik. Though no subject had a reported magnesium value which exceeded the standard definition of hypermagnesemia, missing data as described in Section 8.4.6. did not allow for a complete exclusion of clinical symptoms associated with this finding.

Three subjects experienced markedly abnormal glucose values during the study. Of these two subjects received Prepopik 1 sachet x 2 (one in the 9-12-year cohort and one in the 13-16 cohort) and one subject received PEG (13-16-year cohort). This is consistent with a known class effect in pediatric patients of ingestion of a noncaloric product during a time of peri-procedure fasting. There were no adverse events associated with the abnormal glucose values.

Although a 1.9-fold increase in exposure was noted compared to the adult population after administration of the same dose of Prepopik, the increased exposure was not associated with corresponding adverse events in subjects where exposure data was captured within the trial or on pharmacodynamic modeling for those where exposure data was not available. Additionally, reduction in total adverse events or orthostatic changes were not seen with the administration of the lower ½ sachet x 2 dose of Prepopik, indicating that a safety benefit was not associated with the lower dose.

Despite the limitations created by missing data; orthostasis, hypoglycemia, and transient shifts in electrolytes including serum magnesium were identified during this review as potential pediatric safety signals. The current labeling should be updated to reflect these findings.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not needed for this 505(b)(2) NDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

FDA recommendations were accepted by the Applicant, including:

- **Contraindications**: Substitution of "Hypersensitivity" in place of "Known Allergies"
- **Section 2 Dosing and Administration**: Updates to be consistent with the Instructions for Use
- **Section 5 Warnings and Precautions/5.1 Serious Fluid and Electrolyte Abnormalities**: Addition of a description of the increased rate of orthostatic change observed in pediatric patients following administration of Prepopik vs the comparator, PEG
- **Section 6 Adverse Reactions/6.1 Clinical Trials Experience**: Addition of a description of clinical trial data from Study 000103 under a Pediatric subheading
- **Section 6.2 Postmarketing Experience**: Substitution of "Anaphylaxis" in place of (b) (4) "
- **Section 8 Use in Specific Populations/8.4 Pediatric Use**: Expansion to describe appropriate pediatric use and cautions advised, specifically the potential for hypoglycemia
- **Section 12 Clinical Pharmacology/12.3**: Pharmacokinetics: Inclusion of pediatric pharmacokinetic data
- **Section 14 Clinical Studies**: Description of efficacy seen in patients 9-16 years of age in Study 000103
- **Section 16 How Supplied/Storage and Handling**: Updates to include information on temperature excursion range
- **Medication Guide and Instructions for Use**: Formatted to follow the Clenpiq label

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

12. Postmarketing Requirements and Commitments

At the time of this review, no additional postmarketing requirements or commitments are recommended by the clinical team.

Appendices

12.1. References

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12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 000103

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 10		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 10		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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