Clinical Review
Sandhya Apparaju, Ph.D.
NDA 209589
CLENPIQ™ (sodium picosulfate, magnesium oxide and citric acid) pre-mixed oral solution

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Glossary

ADI  Acceptable Daily Intake
AE  Adverse Event
AESI  Adverse Events of Special Interest
ANDA  Abbreviated New Drug Application
BHPM  Bis-(p-hydroxyphenyl)-pyridyl-2-methane
BW  Body Weight
CDER  Center for Drug Evaluation and Research
CFR  Code of Federal Regulations
CMC  Chemistry Manufacturing and Controls
CT  Computed Tomography
DARRTs  FDA Document Archiving Reporting and Regulatory Tracking System
DGIEP  Division of Gastroenterology and Inborn Errors Products
DP  Drug Product
DPMH  Division of Pediatric and Maternal Health
DPV  Division of Pharmacovigilance
ECG  Electrocardiogram
EDTA  Ethylene diamine tetra acetic acid [specifically, Disodium Edetate in this review]
EEG  Electro encephalogram
EU  European Union
FAERS  FDA Adverse Event Reporting System
FDA  Food and Drug Administration
g  gram
GI  Gastrointestinal
GMP  Good Manufacturing Practice
h  hour
IND  Investigational New Drug Application
iPSP  initial Pediatric Study Plan
Kg  Kilogram
L  Liter
LD  Listed Drug
mg  milligrams
mL  milliliter
mmol  millimoles
MOA  Mechanism of Action
mOsm  milliosmoles
NaCl  Sodium Chloride
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NDA New Drug Application
NF National Formulary
NGT Nasogastric Tube
ODE III Office of Drug Evaluation III
OND Office of New Drugs
OSE Office of Surveillance and Epidemiology
Oz Ounce
PEG Polyethylene Glycol
PEG-ELS Polyethylene glycol Electrolyte Lavage Solution
PeRC Pediatric Review Committee
PMC Post MarketingCommitment
PMR Post Marketing Requirement
PREA Pediatric Research and Equity Act
PT Preferred Term
REMS Risk Evaluation and Mitigation Strategy
SAE Serious Adverse Event
SOC System Organ Class
SPMC Sodium Picosulfate, Magnesium Oxide, Citric Acid
Tid ter in die [3 times a day]
USP United States Pharmacopoeia
V Volume
W Weight
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1 Executive Summary

1.1. Product Introduction

NDA 209589, by Ferring Pharmaceuticals seeks the approval of Clenpiq pre-mixed oral solution in adults. Each bottle contains 10 mg of sodium picosulfate, 3.5 mg of magnesium oxide and 12 g of anhydrous citric acid in 160 mL of solution. The proposed indication is for cleansing of colon as a preparation for colonoscopy. Sodium picosulfate is a stimulant laxative, while magnesium citrate, which is formed by the combination of magnesium oxide and anhydrous citric acid, is an osmotic laxative. Together, the two laxatives produce a purgative effect, which when ingested with additional fluids, produces watery diarrhea.

No new clinical trials were conducted in support of Clenpiq pre-mixed oral solution. This 505(b)(2) NDA relies on the safety and efficacy findings of the listed drug (LD), Prepopik powder for oral solution (sodium picosulfate, magnesium oxide, anhydrous citric acid, NDA 202535), which is also manufactured by Ferring Pharmaceuticals and was approved for adults in 2012. Prepopik is a ‘powder for oral solution’, and the proposed product Clenpiq is a ready-to-drink, pre-mixed, oral solution. Both products have the same active components, and differ with respect to their inactive ingredients, sodium content, and osmolality. The final dosage form (oral solution) and the volume administered (~ 160 mL) to the patient per unit dose are however comparable for both products. The Applicant has submitted a request for a biowaiver for review pursuant to 21 CFR 320.22(b)(3), claiming that the bioequivalence of Clenpiq to Prepopik (NDA #202535) is self-evident.

The proposed indication and dosing regimen for Clenpiq are similar to Prepopik. Clenpiq is a ready-to-drink solution, and therefore there is no initial reconstitution step. The proposed dosing and administration instructions, including ingestion of an additional 40 ounces of clear liquids (five 8-oz cups) are otherwise similar to Prepopik. The dosing regimen includes two doses administered either as the “split-dose” (preferred) or the “day-before” (alternative) regimens, relative to the colonoscopy as described:\footnote{Prepopik- Approved Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202535lbl.pdf}:

Split-Dose Dosage Regimen (Preferred Method)
- First dose: administer during evening before the colonoscopy
- Second dose: administer the next day, during the morning prior to the colonoscopy

Day-Before Dosage Regimen (Alternative Method), if Split-Dosing is inappropriate
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- First dose: administer during afternoon or early evening before the colonoscopy
- Second dose: administer 6 hours later during evening before colonoscopy

Clenpiq is a combination drug product with the active pharmaceuticals ingredients (API) sodium picosulfate, magnesium oxide and anhydrous citric acid (SPMC). Applicants are generally required to provide evidence that each component of the combination makes a contribution to the claimed effects (21 CFR 300.50). During the review of the listed drug Prepopik (NDA 202535), it was determined that DGIEP can rely on literature to support its decision not to require factorial studies, and that the approach fulfills the requirements of the combination policy. That reliance on the literature classified NDA 202535 as a 505(b)(2) application\(^2\). Since Clenpiq is relying upon the approval of Prepopik, and there are no qualitative or quantitative changes to the active drugs in the product (relative to LD), the combination rule is considered to be addressed for this 505(b)(2) NDA.

1.2. **Conclusions on the Substantial Evidence of Effectiveness**

No assessment of effectiveness is warranted for the proposed drug product, as this 505(b)(2) NDA relies upon the findings of efficacy for the LD [NDA 202535, Prepopik]. The applicant has submitted a biowaiver request pursuant to 21 CFR 320.22(b)(3).

1.3. **Benefit-Risk Assessment**

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\(^2\) NDA 202535, CDTL review dated 07/14/2012 by Dr. Robert Fiorentino
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<th>Benefit-Risk Summary and Assessment</th>
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<td>Colonoscopy is the current standard of care for screening/diagnostic purposes, including for colon cancer, and for therapeutic or surgical interventions related to the colonic mucosa. To ensure adequate visualization, the colon needs to be free of any residue and therefore use of a safe and effective bowel cleansing preparation is an essential step ahead of the procedure. There are several FDA-approved bowel cleansing preparations, primarily acting either as an osmotic or a stimulant laxative, or a combination of both. An efficient bowel-cleansing agent should be easy to use, of low volume, and should not cause significant fluid or electrolyte disturbances. Newer agents that offer additional convenience and safety to the patient without compromising on efficacy are always desirable. The proposed formulation, Clenpiq, is a ready-to-drink pre-mixed oral solution of sodium picosulfate, magnesium oxide and anhydrous citric acid (SPMC). No new efficacy trials were conducted in support of this 505(b)(2) NDA. The Applicant is relying upon the established efficacy of the LD Prepopik (powder for oral solution) (NDA 202535). A biowaiver request has been submitted by the Applicant for Clenpiq NDA 209589, which will be granted.</td>
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The colon-cleansing efficacy of Prepopik (LD) was evaluated for non-inferiority against a comparator in two randomized, active-controlled trials in patients scheduled to have an elective colonoscopy. Patients randomized to Prepopik in the two studies were treated with one of two dosing regimens: Split-dose (evening before and day of) [Study 1] or Day-Before (afternoon/evening before only) [Study 2]. The active comparator was a preparation containing two liters of polyethylene glycol plus electrolytes solution (PEG + Electrolytes) and two 5-mg bisacodyl tablets, administered the day before the procedure. The primary efficacy endpoint was the proportion of patients with successful colon cleansing, as assessed by blinded colonoscopists using the Aronchick Scale. In both studies, Prepopik was non-inferior to the comparator. The proportion of patients with successful colon cleansing in Study 1 (Split-Dose) were 84.2 % for Prepopik vs. 74.4 % for the active comparator; for Study 2 (Day-before dosing), these values were 83 % for Prepopik vs. 79.7 % for the active comparator. Thus, the clinical effectiveness of SPMC active drug combination for bowel cleansing has been established in the clinical trials conducted for Prepopik. |

The proposed 505(b)(2) drug product (Clenpiq Oral Solution) contains different inactive ingredients compared to the LD, including malic acid (at amounts higher than in other FDA-approved products) and edetate disodium (EDTA), which are not present in the Prepopik formulation. In addition, the proposed formulation contains sodium hydroxide, The safety of all inactive ingredients has been adequately justified by the Applicant, as deemed by the multi-disciplinary review team for this NDA. The inactive ingredient malic acid is an approved food additive, but not for use in baby foods. The agreed iPSP for Clenpiq waives studies in patients < 1 y/o, thereby avoiding exposure of malic acid in very young infants who are of the age range that would consume baby foods. While the sodium content per unit dose of Clenpiq is higher than from Prepopik |
The potential safety concern of hypocalcemia with use of EDTA in Clenpiq is mitigated, as EDTA salts are poorly absorbed when administered orally. At the anticipated amounts absorbed, the estimated calcium potential of EDTA is low and not expected to cause clinically meaningful hypocalcemia. In addition, the acute use of the proposed drug product for bowel cleansing in preparation for colonoscopy (once or twice a year) alleviates concerns that typically arise with chronic exposure to drug product components, following long-term or daily use.

The Clenpiq pre-mixed oral solution has an approximately 3-fold higher osmolality compared to reconstituted Prepopik powder for oral solution (1269 vs. 441 mOsm/kg). This high osmolality is not anticipated to cause esophageal irritation, as alcoholic and non-alcoholic beverages with similarly high osmolality are regularly consumed in a volume comparable to Clenpiq dose (160 mL). Examples of such beverages include white wine (2677 mOsm/kg), prune juice (1174 mOsm/kg), cranberry juice (907 mOsm/kg) and Pepsi-Cola (716 mOsm/kg). In addition, the Applicant has demonstrated by means of \textit{in situ} experiments that the final osmolality values for the proposed and listed formulations were comparable after the initial dose was sequentially diluted in gastric/intestinal fluids, and in up to 40 ounces of additional fluids, as directed in the labeling for both products.

The risks associated with the API drug combination (SPMC) were adequately described in the clinical trials for the LD, Prepopik. The most common adverse reactions (>1%) for Prepopik are listed as nausea, headache and vomiting. Serious fluid and serum electrolyte abnormalities, seizures secondary to fluid/electrolyte disturbances, increased risk for renal injury in patients with renal impairment, rare reports of cardiac arrhythmias are reported in Warnings section of Prepopik labeling. Post-marketing experience also identified cases of hypersensitivity reactions, gastrointestinal and neurological symptoms. A FAERS search by DPV during the review of NDA 209589 identified several cases of ‘altered consciousness’ following administration of SPMC products. Due to a clear temporal association of the cases with the drug product administration, ‘altered consciousness’ and related terms of confusion, delirium, and loss of consciousness, are recommended for addition to the proposed Prescribing Information (section 17- Patient Counseling Information) and the Medication Guide for Clenpiq. Overall, the benefit-risk profile for Clenpiq is not expected to be significantly different from that of Prepopik, and appears favorable.
2 Therapeutic Context

2.1. Analysis of Condition

Colonoscopy is the current standard of care for screening/diagnostic purposes, including for colon cancer, and for therapeutic or surgical interventions related to the colonic mucosa. To ensure adequate visualization of the colon for presence of bleeding, inflammation, or abnormal growths such as adenomas, polyps, tumors and to minimize procedural complications (e.g., perforation, sepsis) and repetitions, the bowel needs to be free of fecal material and debris prior to colonoscopy. Thus, use of a safe and effective bowel cleansing preparation is an essential step ahead of the procedure. Since colon cleansing typically occurs in an outpatient setting, such products should be easy to use, safe, well tolerated and should not result in significant fluid or electrolyte disturbances. In addition, patient convenience, comfort and product palatability are important for ensuring treatment compliance and adequate colon cleansing.

Compounds used for bowel cleansing can be divided into 3 categories per their mechanism of action: isosmotic, hyperosmotic and stimulant. Their physiologic mechanisms affect the choice of preparation, especially in patients with underlying comorbidities, and in vulnerable populations including the pediatric and geriatric groups.

Isosmotic preparations that contain polyethylene glycol (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 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 in combination with sodium picosulfate (a stimulant laxative) is approved as Prepopik under NDA 202535 as a bowel cleansing agent in preparation for colonoscopy.

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

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  Summary of Approved Therapies for Colon Cleansing as a Preparation for Colonoscopy

<table>
<thead>
<tr>
<th>Tradename; Sponsor</th>
<th>Active Ingredient(s)</th>
<th>Other inactive ingredients (and amounts)</th>
<th>Approved ages, formulation and Mechanism of Action</th>
<th>Indication and dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOVIPREP NDA 021881 Salix Pharms</td>
<td>4 separate pouches (2 of pouch A and 2 of pouch B). Pouch A: 100 g of PEG 3350, 7.5 g of sodium sulfate, 2.691 g of sodium chloride, and 1.015 g of potassium chloride. Pouch B: 4.7 g of ascorbic acid, and 5.9 grams of sodium ascorbate, USP.</td>
<td>Aspartame, NF (sweetener), acesulfame potassium, NF (sweetener), and lemon flavoring (in pouch A)</td>
<td>18 years or older Powder for solution Osmotic laxative</td>
<td>Cleansing of the colon as preparation for colonoscopy 2 regimens: Split-dose (2-day)- preferred Evening only (1-day)</td>
</tr>
<tr>
<td>OSMOPREP NDA 021892 Salix Pharms</td>
<td>1.102 g sodium phosphate monobasic monohydrate, 0.398 g sodium phosphate dibasic anhydrous; for a total of 1.5 g of sodium phosphate per tablet</td>
<td>Polyethylene glycol 8000, NF and magnesium stearate, NF</td>
<td>18 years or older Tablet Osmotic Laxative</td>
<td>Cleansing of the colon as preparation for colonoscopy Evening before colonoscopy: Four tablets with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets Next morning: Four tablets with 8 ounces of clear liquids every 15 min for a total of 12 tablets</td>
</tr>
<tr>
<td>NULYTELEY NDA 19797 Braintree</td>
<td>420 g PEG3350, 5.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride</td>
<td>One 2.0 g flavor pack (optional)</td>
<td>Use in children younger than 2 years of age should be carefully monitored. Studies support use down to 6 months of age.</td>
<td>Cleansing of the colon in preparation for colonoscopy in adults and pediatric patients aged 6 months or greater Early in the evening prior to colonoscopy, instruct</td>
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</table>
| GOLYTELY  NDA 019011  Braintree | Disposable jug contains: 236 g PEG 3350, 22.74 g sodium sulfate (anhydrous), 6.74 g sodium bicarbonate, 5.86 g sodium chloride and 2.97 g potassium chloride  
Packet form contains: PEG3350 227.1g, sodium sulfate (anhydrous) 21.5 g, sodium bicarbonate 6.36 g, sodium chloride 5.53 g, potassium chloride 2.82 g | Pineapple flavoring | Adults  
Powder for solution  
Osmotic laxative | Cleansing of the colon in preparation for colonoscopy and barium enema X-ray examination in adults  
Early in the evening prior to colonoscopy  
Adults: Drink at a rate of 240 ml (8 oz.) every 10 minutes, until 1 gallon is consumed or rectal effluent is clear. For NGT, the rate is 1.2 to 1.8 L/h |
<p>| TRILYTE | 420 g PEG 3350, 3.22 g Flavor | Use in children | Bowel cleansing prior to |</p>
<table>
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<th>Tradename; NDA #; Sponsor</th>
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<tr>
<td>ANDA 076491 Mylan Pharms</td>
<td>5.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride</td>
<td>packs</td>
<td>younger than 2 years of age should be carefully monitored. Studies support use down to 6 months of age. Powder for solution Osmotic laxative</td>
<td>colonoscopy Can be used on the morning of the procedure or the evening before: Adults: At a rate of 240 mL (8 oz.) every 10 minutes, until the rectal effluent is clear or 4 L are consumed. Pediatric Patients (aged 6 months or greater): At a rate of 25 mL/kg/hour, until the rectal effluent is clear. NGT Administration: Adults: At a rate of 20-30 mL per minute (1.2-1.8 liters per hour) Pediatric Patients (aged 6 months or greater): At a rate of 25 mL/kg/hour, until the rectal effluent is clear.</td>
</tr>
<tr>
<td>COLPREP Kit NDA 204553 Gator Pharms</td>
<td>One ColPrep Kit contains two 200 ml bottles; Each bottle contains sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.</td>
<td>Citric acid anhydrous, sucralose, and lemon flavor</td>
<td>Adults Powder for Solution Osmotic laxative</td>
<td>Cleansing of the colon as a preparation for colonoscopy in adults Recommended dosage: split-dose (2-Day) oral regimen: Dose 1: administered in the evening before colonoscopy, 10 to 12 h before the second dose Dose 2: administered the morning of colonoscopy, at least 3 ½ hours before colonoscopy</td>
</tr>
<tr>
<td>Monobasic sodium phosphate and dibasic sodium phosphate</td>
<td>1.102 g of monobasic sodium phosphate, and 0.398 g of dibasic sodium</td>
<td>Polyethylene glycol 8000; and magnesium stearate</td>
<td>18 years and older Tablet Osmotic laxative</td>
<td>For cleansing of the colon as a preparation for colonoscopy The evening before the colonoscopy procedure:</td>
</tr>
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</table>
| ANDA 079247 Novel Labs (Discontinued) | phosphate | | | Take 4 tablets with 8 oz of clear liquids every 15 min for a total of 20 tablets.  
On the day of colonoscopy procedure:  
Starting 3-5 hours before the procedure, take 4 tablets with 8 oz of clear liquids every 15 min for a total of 12 tablets. |
| SUPREP BOWEL PREP NDA 022372 Braintree labs | Two 6 ounce bottles  
Each bottle contains: sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g. | Sodium benzoate, sucralose, malic acid, citric acid, flavoring ingredients, purified water | Adults  
Oral Solution  
Osmotic laxative | Cleansing of the colon in preparation for colonoscopy  
Split Dose (2-Day) Regimen  
Evening before colonoscopy: dilute one bottle with water to a total volume of 16 oz. and drink the entire amount. Drink 32 oz of water over the next hour.  
Next morning: repeat both steps using the second bottle. |
| COLYTE with flavor packs NDA 018983 Mylan Specialty | PEG 3350 240 g, sodium chloride 5.84 g, potassium chloride 2.98 g, sodium bicarbonate 6.72g, sodium sulfate (anhydrous) 22.72g | 3.22 g flavor pack contains: hypromellose, natural and artificial flavor powder, saccharin sodium, colloidal silicon dioxide | Adults  
Powder for Solution  
Osmotic laxative | For bowel cleansing prior to colonoscopy or barium enema X-ray examination  
Recommended adult oral dose is 240 ml (8 fl. oz.) every 10 minutes.  
Lavage is usually complete after the ingestion of 3 - 4 liters.  
NGT: Colyte with flavor packs is administered at a rate of 20 - 30 ml/min (1.2 - 1.8 l/h) |
### Clinical Review

**Sandhya Apparaju, Ph.D.**

NDA 209589

**CLENPIQ™ (sodium picosulfate, magnesium oxide and citric acid) pre-mixed oral solution**

<table>
<thead>
<tr>
<th>Tradename; NDA #; Sponsor</th>
<th>Active Ingredient(s)</th>
<th>Other inactive ingredients (and amounts)</th>
<th>Approved ages, formulation and Mechanism of Action</th>
<th>Indication and dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halflutely; NDA 21551 Braintree (Discontinued)</td>
<td>5 mg bisacodyl tablet and powder for reconstitution containing: 210 g of PEG-3350, 2.86 g of sodium bicarbonate, 5.6 g of sodium chloride, 0.74 g of potassium chloride</td>
<td>(b) (4)</td>
<td>For use in adults</td>
<td>For cleansing of the colon as a preparation for colonoscopy on the day prior to colonoscopy: Take one 5 mg bisacodyl delayed-release tablet with water Wait for a bowel movement (or maximum of 6 hours) then drink the 2 liter Halflutely solution at a rate of 8 oz every 10 minutes</td>
</tr>
<tr>
<td>Prepopik NDA 202535 FERRING Pharms</td>
<td>10 mg sodium picosulfate, 3.5 g magnesium oxide and 12 g anhydrous citric acid</td>
<td>Potassium hydrogen carbonate, saccharine sodium and orange or cranberry flavors</td>
<td>Adults</td>
<td>For cleansing of the colon as a preparation for colonoscopy Two dosing regimens, each requires two separate dosing times • “Split Dose” method is preferred method; • “Day Before” method is alternative method</td>
</tr>
</tbody>
</table>

PEG: Polyethylene Glycol, NF: National Formulary, NGT: Nasogastric Tube, fl. oz: fluid ounce

Source: Reviewer’s table of approved bowel cleansing preparations; drugs@fda

### 3 Regulatory Background

#### 3.1 U.S. Regulatory Actions and Marketing History

The proposed active drug combination in Clenpiq, i.e., sodium picosulfate, magnesium oxide and anhydrous citric acid (SPMC) is approved in the U.S. as Prepopik powder for oral solution under NDA 202535, (Ferring Pharmaceuticals Inc.), and was approved on 07/16/2012. It is indicated for cleansing of the colon as a preparation for colonoscopy in adults.
3.2. **Summary of Presubmission/Submission Regulatory Activity**

Pre-submission regulatory activities related to the proposed pre-mixed, oral solution containing the same active components as Prepopik [NDA 202535] have been documented under IND 101738 for Prepopik.

A type C guidance meeting between FDA and the Applicant to discuss the proposed oral solution formulation was held on 02/01/2016. During this meeting, FDA agreed that a biowaiver request may be submitted for review. In addition, FDA suggested that sponsor should include toxicological qualification for malic acid (inactive ingredient), as the proposed amount FDA also informed the Applicant that the proposed formulation constitutes a new dosage form and therefore will need to be submitted as a new NDA application, and that it would also trigger Pediatric Research Equity Act (PREA) requirements. A type B pre-NDA meeting to determine the adequacy of the data proposed for NDA filing was held between FDA and the Sponsor on 05/17/2016. During this meeting, FDA informed the Applicant that their proposed NDA will be a 505(b)(2) application because it will cross-reference NDA 202535, a 505(b)(2) application that relied on published literature. FDA also agreed that the lack of available clinical data supporting the oral solution would not be a filing issue and that it would be acceptable to submit the NDA based on a request for a biowaiver. FDA also noted that if a biowaiver is not granted, pharmacokinetics will not be considered as a viable approach for establishing bioequivalence and that the Applicant will need to conduct clinical studies to demonstrate comparable efficacy and safety of the new formulation, with PK as part of the assessments. The non-clinical reviewers concurred that the information proposed for submission is adequate for filing. Extensive advice was provided during this meeting regarding the justification needed for an adequate biowaiver request, and CMC requirements.

An internal meeting with PeRC was held on 06/08/2016 to discuss the iPSP. A Pediatric and Maternal Health (DPMH) review of the proposed pediatric study plan was also finalized in DARRTs on 03/06/2017. An initial agreement on the proposed pediatric study plan was communicated to the Applicant on 10/28/2016 after FDA review. The plan includes a waiver for studies in pediatric patients below 12 months of age, and a deferral for three proposed pediatric studies (age groups: 12 months to less than 2 years, 2 to < 9 years and 9 to 16 years).

3.3. **Foreign Regulatory Actions and Marketing History**

The proposed active ingredient combination (SPMC) is a dual action laxative with osmotic and

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4 Sources: Official meeting minutes and review documents in DARRTs filed under IND 101738

5 IND 101738, FDA correspondence to Sponsor dated 10/28/2016- ‘Pediatric Study Plan-Initial Agreement’
bowel stimulating properties that was initially approved in the United Kingdom in 1980. While the exact formulation of the proposed pre-mixed oral solution is not marketed elsewhere, SPMC (active drug) combination is marketed as a powder for oral solution in several countries including the U.S. under the tradenames of Pico-Salax, Picoprep, Picolax or Prepopik. The Applicant noted that the active drug combination is also approved for pediatric use in the UK, Canada, and in 24 European countries.

In a recent safety update to NDA 202535 (LD)^6, Ferring has reported obtaining marketing rights from Pharmbio Korea, Inc for Picosolution, a pre-mixed, oral solution of the SPMC drug combination. It is approved in Korea for bowel cleaning prior to X-ray examination or endoscopy and prior to surgery, when judged clinically necessary, in both adults and children down to one year of age. The formulation for Picosolution includes (amount unspecified). The Applicant noted in their safety update to the FDA that the formulation of Clenpiq is different from that of Picosolution. Ferring and Pharmbio have a Safety Data Exchange Agreement to share post-marketing and clinical trial pharmacovigilance data.

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

4.1. Office of Scientific Investigations (OSI)

This section is not applicable as no new clinical trials were conducted in support of this NDA and investigations by OSI were not needed.

4.2. Product Quality

The proposed SPMC Oral Solution is a colorless to slightly yellow, clear solution (amount unspecified). It contains 10 mg Sodium Picosulfate, 3.5 g Magnesium Oxide, and 12 g Anhydrous Citric Acid. Although the active ingredients in the Prepopik and Clenpiq formulations are equivalent in terms of quantity, the inactive ingredients differ between the two formulations including a higher sodium concentration, and the presence of malic acid in Clenpiq. Table 2 compares the qualitative and quantitative composition of the proposed and LD products. Please refer to the CMC review of this NDA for details related to product development.

Table 2 Comparative Composition of Prepopik (LD) and Clenpiq (proposed) Oral Solution (per dose)

^6 Source: Clinical safety update dated 05/26/2017 for NDA 202535 [PREPOPIK]
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<table>
<thead>
<tr>
<th>Active Ingredients (per unit dose)</th>
<th>PREPOPIK® Powder for Oral Solution (approved under NDA #202535)</th>
<th>Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid Oral Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium picosulfate</td>
<td>10 mg</td>
<td>Sodium picosulfate</td>
</tr>
<tr>
<td>Magnesium oxide</td>
<td>3.5 g</td>
<td>Magnesium oxide</td>
</tr>
<tr>
<td>Anhydrous citric acid</td>
<td>12 g</td>
<td>Anhydrous citric acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactive Ingredients (per unit dose)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharin sodium</td>
<td>(0)(4)</td>
<td>Sodium benzoate</td>
</tr>
<tr>
<td>Potassium hydrogen carbonate</td>
<td></td>
<td>Sucrose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acesulfame potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edetate disodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium metabisulfite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium hydroxide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0)(4) water</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flavors (per unit dose)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cranberry flavor:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maltodextrin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glyceryl triacetate (triaacetin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium octenyl succinyl starch</td>
</tr>
</tbody>
</table>

Source: Applicant’s Table 1, page 2 of non-clinical module- Introduction (2.6.1)

The proposed and LD products have qualitatively and quantitatively identical active components. They are also identical with respect to the dosing volume, administration instructions, and the route of administration. Despite the difference in the dosage form (Prepopik ‘powder for oral solution’ vs. Clenpiq ‘pre-mixed oral solution’), the final formulation (oral solution) and volume administered by patients is approximately the same for both products. The differences are with respect to qualitative and quantitative composition of their inactive ingredients. Specifically, the new formulation (Clenpiq pre-mixed oral solution) contains several inactive ingredients, namely edetate disodium, malic acid, sodium benzoate, sucrose and acesulfame potassium, sodium metabisulfite and sodium hydroxide. Clenpiq pre-mixed oral solution (160 mL) has an approximately 3-fold higher osmolality compared to Prepopik powder reconstituted in 5 ounces of water [1269 mOsm/kg vs. 441 mOsm/kg]. (See sections 8.5.1 to 8.5.4 of this review for a discussion of these differences from a clinical perspective).

4.2.1. Quality Assessment- Biopharmaceutics

The Biopharmaceutics reviewer for this NDA assessed the formulation differences, including the proposed inactive ingredients, the higher amount of sodium, and a higher osmolality in Clenpiq as compared to Prepopik, and had no specific concerns. Specifically, the reviewer noted that “the existence of high amount of malic acid would not affect laxative function of the proposed...
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Drug product, and would not pose any safety concern”.

Concerning the Applicant’s biowaiver request for the proposed formulation, the biopharmaceutics reviewer concluded that, “The bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product is considered to be established. The submitted biowaiver request is therefore acceptable. From Biopharmaceutics perspective, NDA 209589 is recommended for approval.”

Specifically, the reviewer noted that “The Applicant requested for a waiver of in vivo bioavailability (BA) and bioequivalence (BE) studies pursuant to 21 CFR 320.22 (b) (3):

(i) is an oral solution; and

(ii) contains the same active drug ingredient(s) in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and

(iii) contains no inactive ingredient or other change in formulation from the drug product that is the subject of an approved full new drug application that may significantly affect absorption or systemic or local availability”.

In their Biopharmaceutics review, the reviewers evaluated the data submitted by the Applicant to justify fulfillment of each of the above criteria and concluded that a biowaiver can be granted.

Reviewer Comment: Please refer to the final review dated 10/06/2017 by Drs. Peng Duan and Tien Mein Chen for additional details regarding the acceptability of the proposed inactive ingredients, differences in sodium content, osmolality, and the biowaiver request for CLENPIQ Oral Solution.

4.2.2. Quality Assessment- Chemistry Manufacturing and Controls

Drug Product: The reviewers recommended ‘approval with an expiration dating period of 18 months from the drug product perspective’.

Reviewer Comment: Please refer to the final Drug Product review by Drs.’ Hamid Shafiei and Moo-Jhong Rhee.

Facilities: The reviewers’ overall conclusion was “Adequate’. Reviewers noted that the facilities were “determined acceptable in their identified functions and responsibilities to support approval of NDA 209589 for manufacturing of CLENPIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution.”

Reviewer Comment: Please refer to the final Facilities review by Drs.’ Carl Lee, and B.J. Ryan.
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Microbiology: The reviewer concluded that the “submission is recommended for approval. No outstanding microbiology deficiencies remain. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process”.

Reviewer comment: Please refer to the final microbiology review by Dr. Eric Adeeku.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

The non-clinical reviewers Drs’. Tamal Chakraborti and Sushanta Chakder concluded that ‘All excipients including malic acid and disodium EDTA were found to be safe at the proposed concentrations used in the Clenpiq formulation. Three [ ] impurities [ ] have also been qualified to support the proposed impurity specification. All the leachables identified in the leachable study were also qualified. Overall, there are no nonclinical approvability issues.’

The reviewers stated that “The amounts of all inactive ingredients used in the DP are within the Inactive Ingredients Database (IID) values, except malic acid and cranberry flavor. The amount of cranberry flavor [ ] for cranberry flavor. This DMF was found to be adequate.” In addition, reviewers noted that sucralose is used at a concentration of [ ] which is acceptable as higher amounts of sucralose have been used in other approved bowel preparation products.

Regarding malic acid, reviewers concluded that “Overall, the presence of [ ] of malic acid in 160 mL of Clenpiq oral solution does not appear to raise any safety concern and is acceptable”. Specifically, the reviewers noted that the “NOAEL of 2500 mg/kg/day in rats and 1250 mg/kg/day in dogs offer adequate [ ] margin of safety for [ ] of malic acid from the Clenpiq formulation. It is to be mentioned here that since the NOAEL was the highest tested dose, the NOAEL could be even higher than the highest tested dose.”

Regarding EDTA, the reviewers concluded that the “level of [ ] of disodium EDTA per dose (160 mL) of Clenpiq does not appear to raise any significant safety concern and is acceptable”. Specifically, reviewers noted that “the 2500 mg/kg/day dose used in the subchronic toxicity study in rats provides approximately [ ]-fold margin of safety for the disodium EDTA exposure of [ ] from Clenpiq.”

In addition, based on their review of a study conducted in rats with oral treatment of Prepopik.
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powder for solution or Clenpiq oral solution, reviewers concluded that the two formulations appeared to be comparable with respect to the pharmacological (laxative) effects.

Reviewer Comment: Overall, the nonclinical reviewers of this NDA did not identify significant safety issues concerning the proposed Clenpiq oral solution formulation. Please refer to the final review in DARRTs dated 10/13/2017 for detailed information including nonclinical justification regarding inactive ingredient safety especially as it relates to safety assessment of malic acid as well as comparability of pharmacological activity for the proposed vs. LD formulations.

4.5. Clinical Pharmacology

The reviewers concluded that the “Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint. The labeling of the clinical pharmacology related information is the same as in the labeling of the reference product and acceptable.”

The reviewers noted that in support of the biowaiver request, the Applicant conducted three in vitro Caco-2 permeability studies. While the reviewers deferred the acceptability of the biowaiver request to the Division of Biopharmaceutics, they concluded that their review of the in vitro Caco-2 studies supports the biowaiver request.

Additionally, the reviewers also noted that the differences in the dosage forms are not expected to significantly affect the bioavailability of the active ingredients between the test and reference products.

Reviewer Comment: Please refer to the final Clinical Pharmacology review by Drs’ Xinyuan Zhang and Insook Kim for additional details.

4.5.1. Mechanism of Action

As per the Prepopik package insert.

4.5.2. Pharmacodynamics

As per the Prepopik package insert.

4.5.3. Pharmacokinetics

As per the Prepopik package insert.

4.6. Devices and Companion Diagnostic Issues

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This section is not applicable as there are no devices or diagnostics associated with this NDA.

4.7. Consumer Study Reviews

No consumer studies were conducted in the context of this 505(b)(2) NDA.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

This section is not relevant, as no clinical trials were conducted in support of this 505(b)(2) NDA.

5.2. Review Strategy

The Applicant is relying upon the safety and efficacy of the LD, Prepopik. Therefore, the following sections of the review template are not relevant for this NDA: Sections 6.0 [Review of relevant individual trials used to support efficacy], 7.0 [Integrated review of effectiveness], specific subsections (8.2, 8.3, 8.4, 8.6, 8.7, 8.8) of Section 8.0 [Review of Safety], and subsection 13.2 [Financial Disclosure].

6 Review of Relevant Individual Trials Used to Support Efficacy

Not applicable. See Section 5.2.

7 Integrated Review of Effectiveness

Not applicable. See Section 5.2.

8 Review of Safety

8.1. Safety Review Approach

No new studies were conducted in support of this 505(b)(2) NDA. Instead the Applicant submitted justification for a biowaver (refer to Biopharmaceutics and Clinical Pharmacology discipline reviews), and proposed to rely upon FDA’s previously established safety and efficacy for the LD, Prepopik [NDA 202535]. The clinical safety assessment of this NDA is described in
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Sections 8.5, 8.9 and 8.11 of this review and includes the following elements:

1. Review of published scientific information for new safety information pertaining to the active moieties and the proposed inactive ingredients in the oral solution, including malic acid and EDTA.
2. Review of publicly available information to justify proposed vs. listed drug product differences concerning the total sodium content and osmolality.
3. Search of FAERS database for the active moieties as conducted by OSE/DPV I.
4. Review of the clinical safety updates submitted to Prepopik NDA 202535.

8.2. **Review of the Safety Database**

Not applicable. See Section 5.2.

8.3. **Adequacy of Applicant’s Clinical Safety Assessments**

Not applicable. See Section 5.2.

8.4. **Safety Results**

Not applicable. See Section 5.2.

8.5. **Analysis of Submission-Specific Safety Issues**

As noted in Section 4.2 - Product Quality, the proposed and listed formulations differ primarily in their inactive ingredients. The sections below address the safety evaluation of relevant inactive ingredients from a clinical perspective. The Applicant has included justification for the safety of inactive ingredients from a non-clinical perspective. Please refer to the non-clinical review of this NDA.

8.5.1. **Malic Acid**

Malic acid is an organic compound with the molecular formula C₄H₆O₅. Malic acid has two stereoisomeric forms (L- and D-enantiomers), of which only the L (+)-isomer exists naturally in various foods. Racemic malic acid (DL-malic acid) is produced industrially and is used as an acidulant in numerous types of candy, food and beverages. Malic acid is an ingredient in Clenpiq Oral Solution, where it amounts to . Two 160 mL doses of Clenpiq, each containing of malic acid, are proposed for administration within a 24-hour
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period for bowel cleansing prior to colonoscopy. Because, the concentration of malic acid in Clenpiq oral solution
the Applicant has submitted a safety assessment of DL-
malic acid for nonclinical review to support the safety of the proposed amount. Please refer to
the nonclinical review by Tamal Chakraborti in this regard.

Unlike L(+)-Malic acid, which is the naturally occurring enantiomer and is integrated as an
intermediary in various metabolic pathways such as Krebs cycle, the fate of unnatural D(-)-Malic
acid component of the racemate is unclear. Thus, some concern has been expressed about the
ability of young infants to metabolize D-malic acid, and the unknown clinical sequelae from a
potential systemic accumulation. The Select Committee on GRAS Substances (SCOGS) Opinion
on Malic acid concluded that “For individuals beyond the age of infancy, there is no evidence in
the available information on L-malic acid and DL-malic acid that demonstrates or suggests
reasonable grounds to suspect a hazard to the public when they are used at levels that are now
current or that might reasonably be expected in the future.” The Joint FAO/WHO Expert
Committee on Food Additives proposed that while no limit should be set for the Acceptable
Daily Intake (ADI) of L-malic acid in humans, good manufacturing limits were set for the D-
isomer. In evaluating the acceptance of malic acid, emphasis was placed on the fact that it is a
natural form, its well-established metabolic pathway and the daily consumption of malic acid-
containing foods. However, the committee noted that the utilization in the body of the D (-)
isomer of malic acid is not well understood. A limitation of use was recommended by the
committee that neither the D (-) nor DL-malic acid should be added to food for very young
infants, except for therapeutic purposes. This is also reflected in the CFR.

Per 21CFR§184.1069 Malic acid, the amount of DL-Malic acid allowed in various food products
(GMP limits) are: processed fruits and fruit juices (3.5 %), nonalcoholic beverages (3.4 %), hard
candy (6.9 %), chewing gum (3 %) etc. In comparison, exposure to malic acid resulting
from Clenpiq, administered as two doses over 24 h is estimated as

The absolute amount of malic acid (in grams) however, is likely to be lower in younger patients (< 12 y/o) at compared to the
adult or adolescent exposure of

References:
7 https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm260468.htm
9 Malic, dl-acid (FAO Nutrition Meetings Report Series 40abc)
10 Final Report on the Safety Assessment of Malic Acid and Sodium Malate, International Journal of Toxicology,
11 https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm260468.htm
12 21CFR §184.1069 Malic acid
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The agreed iPSP for CLENPIQ pre-mixed oral solution proposes clinical trials in pediatric patients who are > 12 months of age, thus excluding exposure in young infants who would be expected to be of an age to consume baby foods, which is in accordance with 21 CFR § 184.1069. While, the malic acid exposure potential in adults or pediatric patients is higher than that approved for common fruit/non-alcoholic beverages, Clenpiq is used once or twice in a year prior to colonoscopy, in contrast to long term exposure via food and beverages.

Reviewer Comment: Overall, there are no significant clinical concerns at this time with the quantities of malic acid in Clenpiq. Malic acid is an accepted additive for daily consumption. The anticipated exposure of malic acid from Clenpiq is somewhat higher than that approved for commonly used beverages. However, the proposed product is intended for single use prior to a scheduled colonoscopy and therefore does not create a potential for long-term exposure to the inactive ingredient that occurs from food or beverages. The Applicant provided additional justification for the safety of Malic Acid in the form of nonclinical studies using malic acid. In this regard, please refer to the nonclinical review of NDA 209589 by Dr. Tamal Chakraborti.

8.5.2. Edetate Disodium (EDTA)

Clenpiq pre-mixed oral solution contains EDTA per 160 mL bottle. The total EDTA exposure per proposed adult dose (2 bottles) is over 24 hours, in a single use setting for bowel cleansing prior to colonoscopy. Published literature suggests that 2% - 5% of EDTA salts are systemically absorbed when taken via the oral route.\(^{13,14,15}\) Assuming that 5% of orally administered EDTA is systemically absorbed, approximately 1% of available ionized serum calcium would be estimated to be in an adult patient (60 kg BW). The estimated EDTA exposures and calcium potential are shown in pediatric subjects (assuming 5% absorption of oral EDTA) in Table 3.

\(^{13}\) The metabolism of C\(^{14}\) labeled ethylenediaminetetra-acetic acid in human beings. Foreman et al, J Lab Clin Med. 1954 Apr;43(4):566-71
\(^{14}\) Lactulose, 51 Cr-labelled ethylenediaminetetra-acetate, L-rhamnose and polyethyleneglycol 500 as probe markers for assessment in vivo of human intestinal permeability, D.G. Maxton et al, Clinical Science (1986) 71, 71-80
\(^{15}\) Measurement of intestinal permeability using 51cr-EDTA, Peled et al, American Journal of Gastroenterology, 1985
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To provide clinical context for the estimated changes in ionized calcium, normal and low ranges of serum calcium are described below. Serum calcium ranges are comparable between children and adults, with reference ranges differing somewhat across data sources. The normal range of total serum calcium is 8.5 - 10.5 mg/dL (2.2 - 2.6 mmol/L) and ionized (free) serum calcium is 4.5 - 5.6 mg/dL (1.1-1.4 mmol/L). In U.S. medical centers, mean (± SD) critical ‘low’ ionized calcium limits were 0.82 ± 0.14 mmol/L (or 3.29 ± 0.56 mg/dL). The accepted critical ‘low’ ionized calcium level in pediatric hospitals appears to be < 0.8 mmol/L\(^{16,17}\). Critical low values of serum calcium - total (free) per Delmar’s Guide to Laboratory and Diagnostic Tests is as follows\(^{18}\):

- Less than 2 mg/dL (< 0.5 mmol/L) may produce tetany or life-threatening complications.
- In patients with multiple blood transfusions, 2-3 mg/dL (< 0.5-0.75 mmol/L) may require calcium administration.

According to published ranges of serum calcium, reduction of ∼ 30 % from low-normal baseline is considered critically low in pediatric patients, with a more than 50 % reduction resulting in life-threatening complications. Therefore, an approximately 0.5- < 3 % reduction of serum free calcium levels based on the EDTA dose from Celenpiq oral solution would not be expected to cause clinically meaningful hypocalcemia.

The nonclinical reviewer for this NDA indicated a margin of safety for disodium EDTA from the adult animal data. The reviewer noted also that since this product will be administered one time before colonoscopy, that there are no expected safety concerns for

\(^{17}\) Don-Wauchope et al, Clinical Biochemistry, 2009.
\(^{18}\) Delmar’s Guide to Laboratory and Diagnostic Tests (2nd edition, 2010)
Reviewer Comment: The informal calcium estimates after a single oral use of Clenpiq in adult and pediatric patients at relevant doses do not appear to raise a significant safety concern. The low absorption potential of orally administered EDTA salts results in an estimated calcium potential that would not be expected to cause clinical manifestations of hypocalcemia as discussed above. In addition, the single use setting of the proposed product for colon cleansing prior to colonoscopy also mitigates concerns regarding accumulation and adverse effects that may be associated with chronic exposure. Therefore, the amount of EDTA in the proposed product does not appear to pose a significant clinical concern at this time. Please refer to nonclinical review of this NDA for safety assessment of EDTA in Clenpiq at the proposed amounts.

8.5.3. Osmolality

As noted earlier in this review, 160 mL of Clenpiq pre-mixed oral solution has approximately a 3-fold higher osmolality compared to 150 ml (or 5 oz) of reconstituted Prepopik [1269 mOsm/kg vs. 441 mOsm/kg]. Per the Dosage and Administration section of the proposed labeling, the Clenpiq pre-mixed oral solution (160 mL) is to be swallowed prior to intake of additional fluids; therefore, esophageal irritation (e.g., nausea, vomiting) that could result from direct exposure of the pre-mixed oral solution represents a potential safety concern. However, while the Clenpiq formulation has a higher osmolality in comparison with Prepopik, similar osmolalities are observed with commonly ingested beverages19, including white wine (2677 mOsm/kg), prune juice (1174 mOsm/kg), cranberry juice (907 mOsm/kg) and Pepsi-Cola (716 mOsm/kg). Therefore, direct ingestion of a 160ml amount of the proposed pre-mixed product would not be expected to result in esophageal irritation.

The Applicant also claims that the osmolality differences between the proposed and the listed drug products will be transient in that they will dissipate upon dilution in the gastrointestinal fluids and with the consumption of additional clear liquids as part of the bowel preparation regimen. The results of the in situ osmolality experiments conducted by the Applicant are summarized in Table 4. The osmolality of Clenpiq pre-mixed oral solution was measured at different points as follows: 1) ‘neat’ or undiluted, 2) following serial dilution in simulated gastric fluid (SGF), 3) following serial dilution in simulated intestinal fluid (SIF), and 4) after up to five 8-ounce portions (as per labeled dosing instructions) of low- and high-osmolality beverages. Osmolality values are shown in comparison to the LD, Prepopik. The data suggests that dilution of Clenpiq pre-mixed oral solution with low osmolality clear liquids (e.g. water, Jell-O,

19 Relationships between the acidity and osmolality of popular beverages and reported postprandial heartburn. Feldman and Barnett, Gastroenterology 1995; 108: 125-131

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Gatorade) reduced the in situ osmolality of the formulation to iso-osmoticity or iso-tonicity after 1-2 glasses. Dilution with high osmolality clear liquids (white grape, apple or white cranberry juices) resulted in a somewhat higher osmolality after ingestion of additional liquid; however, these findings were comparable for the proposed and listed products.

Table 4  Osmolality (mOsm/kg) of Prepopik and Clenpiq after Sequential Dilution of SGF/SIF and Clear Liquids of Low and High Osmolalities

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolality (mOsm)</th>
<th>Neat</th>
<th>50 mL SGF</th>
<th>100 mL SIF</th>
<th>8 ounce glasses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Low Osmolality Liquids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPOPIK®</td>
<td>441</td>
<td>385</td>
<td>300</td>
<td>176</td>
<td>146</td>
</tr>
<tr>
<td>CLENPIQ™</td>
<td>1269</td>
<td>1014</td>
<td>730</td>
<td>376</td>
<td>289</td>
</tr>
<tr>
<td>Jell-O (82 mOsm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPOPIK®</td>
<td>441</td>
<td>385</td>
<td>300</td>
<td>213</td>
<td>185</td>
</tr>
<tr>
<td>CLENPIQ™</td>
<td>1269</td>
<td>1014</td>
<td>730</td>
<td>389</td>
<td>302</td>
</tr>
<tr>
<td>Gatorade (139 mOsm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPOPIK®</td>
<td>441</td>
<td>385</td>
<td>300</td>
<td>139</td>
<td>88</td>
</tr>
<tr>
<td>CLENPIQ™</td>
<td>1269</td>
<td>1014</td>
<td>730</td>
<td>316</td>
<td>205</td>
</tr>
<tr>
<td>Tap Water (18 mOsm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPOPIK®</td>
<td>441</td>
<td>385</td>
<td>300</td>
<td>765</td>
<td>876</td>
</tr>
<tr>
<td>CLENPIQ™</td>
<td>1269</td>
<td>1014</td>
<td>730</td>
<td>950</td>
<td>1000</td>
</tr>
<tr>
<td><strong>High Osmolality Liquids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPOPIK®</td>
<td>441</td>
<td>385</td>
<td>300</td>
<td>574</td>
<td>644</td>
</tr>
<tr>
<td>CLENPIQ™</td>
<td>1269</td>
<td>1014</td>
<td>730</td>
<td>764</td>
<td>774</td>
</tr>
<tr>
<td>Cranberry Juice (563 mOsm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREPOPIK®</td>
<td>441</td>
<td>385</td>
<td>300</td>
<td>344</td>
<td>353</td>
</tr>
<tr>
<td>CLENPIQ™</td>
<td>1269</td>
<td>1014</td>
<td>730</td>
<td>522</td>
<td>458</td>
</tr>
</tbody>
</table>

Source: Applicant-submitted Table 11 (page 24 of 33), 1.12.15: Request for Biowaiver [NDA 209589; 01/31/2017]

Please refer to the biopharmaceutics review for additional information on the simulations performed and the assessment of osmolality differences. The biopharmaceutics reviewer also
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noted that the osmolality in Clenpiq (~1269 mOsm/kg) is not unusually higher as it is within the range of commonly ingested beverages and hence would not pose any safety risks.

Reviewer Comment: The high osmolality of the initial dose of Clenpiq pre-mixed oral solution is not anticipated to result in esophageal irritation, as regularly consumed beverages such as white grape, cranberry, prune juices, white wine etc., have a similarly high osmolality. In addition, the initial high osmolality of Clenpiq pre-mixed oral solution appears to dissipate with sequential dilution in GI fluids and ingestion of additional clear liquids such as tap water, Gatorade, or Jello. While the osmolality remained high with clear liquids such as white grape, cranberry or apple juices due to the inherent high osmolality of these beverages, the measured osmolalities after the intake of additional fluids (40 ounces, as five 8-oz glasses) were similar for the approved Prepopik (LD) when measured with such beverages. The final osmolality of Clenpiq, when taken as instructed in the labeling, is comparable to that of Prepopik, which is an approved bowel cleansing formulation. Thus, there appear to be no safety concerns about osmolality from a clinical perspective.

8.5.4. Sodium Content

The sodium content contained in a single dose of Clenpiq oral solution is higher than that contained in a single dose of Prepopik. The Applicant noted that the amount of sodium in Clenpiq is less than the sodium from other approved bowel cleansing preparations, such as Moviprep, Suprep, GoLytely, and NuLytely.

Because the proposed formulation relies upon the approval of Prepopik, it is important to assess whether the higher sodium content in Clenpiq could potentially impact both the efficacy and safety of the active drug combination (SPMC). The biopharmaceutics review addresses the concern related to efficacy, by stating the following regarding drug absorption: "...of the sodium in CLENPIQ comes from [blank], which is functioned..."

Please refer to the finalized biopharmaceutics review by Dr. Duan for details in this regard.

The potential impact of a higher sodium content was also evaluated from a safety standpoint. From a clinical perspective, although the total amount of sodium per unit dose of Clenpiq is higher compared to that in Prepopik, it is lower than the sodium resulting from other approved bowel cleansing formulations. The 2010 Dietary Guidelines for Americans (DGA) recommends that all Americans should limit their sodium intake to <2.3 g/day; individuals aged ≥51 y, African Americans, and those with hypertension, diabetes, or chronic kidney disease should
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further reduce their intake to 1.5 g/day\textsuperscript{20}. The amount of sodium in Clenpiq is higher than the recommended daily intake; however, it is well within the range of the American diet which may provide over 3.4 g of sodium per day\textsuperscript{21}, primarily from the consumption of packaged/processed or restaurant foods. In addition, the proposed single use administration of bowel cleansing preparations, administered typically once or twice in a year prior to colonoscopy, mitigates the concern that may otherwise arise with chronic exposure to large amounts of sodium.

Reviewer comment: The sodium content in Clenpiq is lower than the sodium content in other approved bowel cleansing formulations, and is also within the range for the average sodium intake from a typical American diet. In addition, this bowel preparation is not indicated to be used chronically, and would typically be given as a single use administration, once or twice a year. Therefore, from a clinical perspective, the sodium content in Clenpiq does not appear to represent a significant safety concern.

8.6. Safety Analyses by Demographic Subgroups

Not applicable. See Section 5.2.

8.7. Specific Safety Studies/Clinical Trials

Not applicable. See Section 5.2.

8.8. Additional Safety Explorations

Refer to section 8.5.2 of this review.

\textsuperscript{21} https://www.fda.gov/food/resourcesforyou/consumers/ucm315393.htm
8.8.1. Pediatrics and Assessment of Effects on Growth

The proposed Clenpiq pre-mixed oral solution has the same active components (SPMC) as the approved Prepopik powder for oral solution, albeit with different inactive ingredients. However, because the proposed oral solution formulation is considered a new dosage form, the Pediatric Research and Equity Act (PREA) requiring the conduct of necessary pediatric assessments applies. In this regard, an iPSP for Clenpiq pre-mixed oral solution was agreed upon in an FDA letter to Ferring dated, 10/28/2016 [IND 101738].

Ferring owns both the proposed Clenpiq formulation, as well as the LD formulation, Prepopik. Pediatric clinical trials under PREA are currently ongoing for Prepopik powder for oral solution (NDA 202535). The agreed iPSP for CLENPIQ proposes identical trials in children ages 1 year and above, and a waiver request for patients < 1 y/o. Ferring is planning to conduct these three studies to evaluate the efficacy and safety of the pre-mixed oral solution formulation in pediatric patients, if FDA considers this necessary after assessment of a biowaiver request [submitted to NDA 209589] and the review of the pediatric trials of Prepopik powder for oral solution. The planned/ongoing safety and efficacy trials of Prepopik powder for oral solution in pediatric patients may, upon FDA review, fulfill the pediatric assessment for the pre-mixed oral solution formulation. Tables 5 and 6 describe the proposed pediatric clinical trials and doses, respectively, of Clenpiq oral solution.

Table 5 Proposed Pediatric Clinical Effectiveness and Safety Studies of CLENPIQ Pre-mixed Oral Solution Formulation
### Table 6

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Type of Study</th>
<th>Comments</th>
<th>Deferral Request Planned for the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - &lt; 1 years old</td>
<td>Waiver requested</td>
<td>1) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age range and is not likely to be used in a substantial number of pediatric patients in this age range</td>
<td>NA</td>
</tr>
<tr>
<td>12 months - &lt; 2 years old</td>
<td>Efficacy and safety study (randomized, assessor-blind, parallel arm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Study to be conducted after approval of the new NDA for pre-mixed oral solution formulation if currently planned pediatric studies assessing the efficacy and safety of Prepopik powder for oral solution in this age group are considered insufficient by the agency after data review</td>
<td>Yes</td>
</tr>
<tr>
<td>2-9 years</td>
<td>Efficacy and safety study (randomized, assessor-blind, parallel arm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Study to be conducted after approval of the new NDA for pre-mixed oral solution formulation if currently planned pediatric studies assessing the efficacy and safety of Prepopik powder for oral solution in this age group are considered insufficient by the agency after data review</td>
<td>Yes</td>
</tr>
<tr>
<td>9-16 years</td>
<td>Efficacy and safety study (randomized, assessor-blind, parallel arm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Study to be conducted after approval of the new NDA for pre-mixed oral solution formulation if currently on going pediatric studies assessing the efficacy and safety of Prepopik powder for oral solution in this age group are considered insufficient by the agency after data review</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA = not applicable

<sup>a</sup> Pre-mixed oral solution formulation will be compared to PEG-based standard of care in each study.

Source: Agreed iPSP (refer to IND 101738, FDA correspondence to Sponsor dated 10/28/2016- ‘Pediatric Study Plan-Initial Agreement’)

**Table 6**  Proposed doses of Clenpiq pre-mixed oral solution for evaluation, shown in comparison to Prepopik pediatric doses in planned/ongoing trials
Reviewer Comment: A biowaiver will be granted for Clenpiq pre-mixed oral solution. In addition, pediatric clinical trials are underway for the LD, Prepopik. The first of these studies in the older pediatric patient cohort (9 – 16 years) is complete and the results will be submitted for review in an efficacy supplement. The elements of the agreed iPSP for Clenpiq, including the revised milestones for study 1 in older pediatric patients (to allow review of Prepopik trial results for this age cohort) were agreed upon during a meeting with PeRC on October 11, 2017 for NDA 209589. The PeRC recommended the Division include the same PREA requirements that were used for Prepopik in the approval letter for this product and inform the sponsor that the PREA requirements for this product will be considered fulfilled if the PREA requirements for Prepopik are fulfilled22.

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 (SPMC): 1) Review of FAERS database, 2) Review of clinical safety updates submitted to NDA 202535 and 3) Review of published literature.

Review of FAERS Database: On DGIEP’s request, OSE/DPV I reviewers completed a search of the FDA Adverse Event Reporting System (FAERS) database for Prepopik powder for oral solution (NDA 202535). Please refer to pharmacovigilance memorandum dated 04/20/2017 by Dr. Lisa Harinstein23. In addition to a broad search of the database, the review also included a

22 10-11-2017 PeRC Minutes
23 Pharmacovigilance memo in DARRTs April 20, 2017 by Dr. Lisa Harinstein, Dr. Eileen Wu, and Dr. Monica Munoz
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search for five adverse events of special interest (AESI): hyponatremia, electrolyte imbalance, seizures/convulsions, ischemic colitis, and ulcerative colitis. The reviewers 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.

The reviewer identified ‘altered consciousness’ as one of the most frequently reported symptoms in cases of hyponatremia. The DPV reviewer notes, “We did identify that altered consciousness was one of the most frequently reported symptoms in the 39 cases of hyponatremia. Although this is a recognized symptom of dehydration, it may be informative to add this symptom to the medication guide to aid in identification of hyponatremia prior to the development of other adverse events, such as seizures.”

There were 8 serious cases of altered consciousness in patients who received SPMC preparation for bowel cleansing prior to elective colonoscopy, with or without additional laxatives. These patients were hospitalized for symptoms of dehydration, severe hyponatremia, and exhibited signs of altered consciousness, such as somnolence, confusion/disorientation, delirium or loss of consciousness.

In addition, there were six other serious cases of ‘altered consciousness’ after administration of SPMC product for bowel cleansing, albeit with confounding factors (concomitant medication or disease). Patients were hospitalized for symptoms of dehydration, severe hyponatremia, and exhibited signs of altered consciousness, such as impaired vigilance, confusion, depressed or loss of consciousness.

Reviewer comment: This reviewer agrees with DPV’s conclusions and recommendation that the term ‘altered consciousness’ and related terms (confusion, delirium and loss of consciousness) to be relevant safety information for communication to patients by means of the Patient Counseling section of the Prescribing Information (17.0) and the MG.

Review of safety updates submitted to NDA 202535 [Prepopik]24:

No clinical trials were conducted to support the NDA application for Clenpiq pre-mixed oral solution, and the exact formulation is not marketed elsewhere. Per pre-NDA agreements the Applicant has cross-referenced the safety updates for Prepopik (submitted to NDA 202535; 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

24 NDA 202535 Clinical Safety Updates for Prepopik Powder for Oral Solution (01/31/2017 and 05/26/2017).
completed clinical trials with the SPMC, foreign approvals, new clinical safety data, post-
marketing safety data, and clinical safety data from published biomedical literature. Overall,
the Applicant noted that there are no significant changes to the safety profile of the active
moieties in Prepopik. The following is a summary of relevant information from the Applicant’s
safety updates:

- 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.

- Recently completed or ongoing clinical trials: Adverse events (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.

Key safety findings from the recent phase 3 trials using the active drug combination were
reported not to identify new safety risks. These included data from three clinical trials
conducted for foreign approvals in China [FE 999169, comparing split-dose SPMC vs. PEG-
Electrolytes], EU [000121, comparing a tailored split-dose SPMC vs. day-before SPMC], Brazil
[000176, split-dose or day-before regimens of SPMC vs. PEG-ELS], and a phase IV trial in Brazil
(trial 000180), comparing Picoprep to oral mannitol and bisacodyl for bowel cleansing). These
studies were not reported to identify new safety signals for SPMC, and no clinically significant
differences were reported in changes from baseline to post-treatment in clinical safety
laboratory values, vital signs, ECG parameters, or physical examination findings.

In their most recent safety update to Prepopik, the Applicant notes that an ongoing phase 3
trial of the Ferring pre-mixed oral solution will be submitted to support regulatory approval in
Canada (000253). This randomized, assessor-blinded, multicenter, trial compares CLENPIQ
(pre-mixed oral solution) to Prepopik(powder for oral solution) in adults. The trial is being
conducted in the US and Canada. As of March 31, 2017, 213 subjects were enrolled.

The Applicant has recently submitted the results of a pediatric clinical trial for Prepopik in
patients 9 to 16 years of age (Trial 000103). The study report is pending review.

Review of published literature: A review of the published literature suggests that in general
the adverse events reported in recent clinical trials generally correspond to the known safety
profile of Prepopik. Few published case reports and abstracts noted electrolyte abnormalities,
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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.

Reviewer Comment: While electrolyte abnormalities and seizures are listed AEs for Prepopik, as discussed earlier in this section, the findings from OSE/DPV I review of FAERS database support the addition of ‘altered consciousness’ to section 17.0 of the PI and to the medication guide.

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 FAERS review by OSE/DPVI identified ‘altered consciousness’ as an indicator for hyponatremia and its sequelae. Hence, this term was to the Patient Counseling (Section 17.0) of the PI and to the MG.

8.10. Additional Safety Issues From Other Disciplines

There are no additional safety issues from other disciplines.

8.11. Integrated Assessment of Safety

NDA 209589 for Clenpiq [sodium picosulfate, magnesium oxide and citric acid, (SPMC)] pre-mixed oral solution is a 505(b)(2) submission relying upon the safety and efficacy of the listed drug, Prepopik powder for oral solution (NDA 202535). The safety of the active drug combination (SPMC) is well established in the proposed target population of adult patients undergoing colonoscopy. There were no new clinical trials submitted in support of Clenpiq, which is a new dosage form for the active drug combination in Prepopik. The two formulations have identical active ingredients, but different inactive ingredients, sodium content and osmolality. The safety of the proposed inactive ingredients, as well as the sodium content and osmolality, in the new pre-mixed oral solution is deemed acceptable from a clinical perspective. A biowaiver request for this formulation was deemed acceptable by the Biopharmaceutics

Reference ID: 4172472
review discipline. The proposed inactive ingredients in Clenpiq were deemed acceptable by the biopharmaceutics and nonclinical review disciplines. This clinical review, therefore primarily focused on assessing the differences in formulation relative to the LD from a safety perspective.

There were several differences/additions of inactive ingredients (i.e., malic acid, EDTA, sodium hydroxide) in the proposed formulation that were evaluated and found to be acceptable from a clinical perspective. The addition of malic acid is justified by the available information on Acceptable Daily Intake (ADI) of this inactive ingredient under GMP in various food products. In addition, L-Malic acid, which occurs naturally, has no limits on daily intake. While, the malic acid exposure potential from Clenpiq is higher than that approved for common fruit/non-alcoholic beverages, the drug product is used once or twice in a year prior to colonoscopy, in contrast to long term exposure via food and beverages. 21CFR184.1069 states that synthetically produced D- and DL-Malic acid should not be used in baby foods. This appears to be based on the concern that the metabolic fate of the D-enantiomer and its accumulation potential upon chronic use and resultant clinical sequela are not well understood. Because the Applicant has requested a waiver for pediatric assessments in patients < 12 months of age, this alleviates the concern regarding use in young infants. This product also contains EDTA per bottle. Orally administered EDTA salts are not well absorbed (1-5 % per published literature), and therefore the calcium potential is estimated to be low. In addition, the proposed drug product is intended for acute or intermittent use, which mitigates concerns regarding potential exposure from chronic or prolonged dosing. From a safety perspective, the EDTA content of Clenpiq does not appear to indicate a safety risk at the proposed amount. The non-clinical reviewers of this NDA have also indicated margin of safety for the proposed amount of EDTA in the drug product. Lastly, the total sodium content in Clenpiq is higher compared to Prepopik; however, it is comparable or lower than the sodium contained in other approved bowel preparation products. And while Clenpiq’s sodium content exceeds the recommended daily intake by FDA, it is within the range of average sodium intake from a typical American diet, and would not be expected to be used chronically. From a safety perspective, the sodium content in Clenpiq appears to be acceptable.

Clenpiq pre-mixed oral solution (160 mL bottle) is to be swallowed prior to intake of additional fluids; therefore, the esophageal irritation (e.g., nausea, vomiting) that could result from direct exposure of the pre-mixed oral solution represents a potential safety concern. However, as several commonly ingested beverages with a similar osmolality do not routinely cause nausea or vomiting, the initial ingestion of ‘neat’ Clenpiq ready-drink solution would also not be expected to cause esophageal irritation. In addition, the observed differences in osmolality (3-fold higher value for Clenpiq pre-mixed solution compared to reconstituted Prepopik) are also expected to be dissipated by serial dilution in GI fluids and additional fluids consumed as part of the dosing regimen, especially low-osmolality beverages such as tap water or Gatorade. Although in the in situ experiments, the osmolality remained high when dosed with inherently high-osmolar fluids such as cranberry juice, white grape juice etc., these values were
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comparable for both Clenpiq and approved Prepopik, if taken as directed in the labeling. The approved labeling for Prepopik recommends ingestion of clear liquids including cranberry, apple or white grape juices. Based on post-marketing experience to date, there appears to be no concern at present with this dosing approach for the Prepopik. Thus, it is reasonable to label Clenpiq the same way.

A review of post-marketing adverse events in the FAERS database by OSE/DPV I identified altered consciousness as a potential precursor to more severe sequelae of hyponatremia, in patients consuming SPMC formulations. A review of the identified cases suggests a temporal association of neurological events during or following the intake of the SPMC drug product. Therefore, inclusion of the term ‘altered consciousness’ and related terms (confusion, delirium, loss of consciousness) in the Patient Counseling section of the PI (17.0) and the Medication Guide is reasonable.

Overall, the risk-benefit of the proposed Clenpiq pre-mixed oral solution for bowel cleansing as a preparation for colonoscopy appears similar to that of the approved listed drug, Prepopik.

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 Prescribing Information

At the time of writing this review, final labeling negotiations with the Applicant are underway. The proposed labeling for Clenpiq is identical to that of the LD, Prepopik (NDA 202535) except for the following:

- Section 2: dosing instructions unique to the premixed oral solution formulation are reflected.
- Section 11: Description of the formulation, including inactive ingredients.
- Section 16: How Supplied
- Section 17: Patient Counseling revised to include the adverse event ‘altered consciousness’.
- Medication Guide: Updated to reflect the addition of ‘altered consciousness’ to the PI. See the final approved version of the Medication Guide.

Please see the approved label for Clenpiq for final agreed upon labeling.
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10.2. Patient Labeling
See Section 10.1.

10.3. Nonprescription Labeling
Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS
Not applicable

11.2. Conditions of Use to Address Safety Issue(s)
Not applicable

11.3. Recommendations on REMS
No REMS were deemed necessary for this 505(b)(2) NDA for CLENPIQ™ oral solution. The benefit risk profile of this product has not changed from that of the currently approved listed drug.

12 Postmarketing Requirements and Commitments

Clenpiq Oral Solution is a new dosage form and therefore this application triggered PREA. Please refer to section 8.8.1 of this review for details. A list of the PREA PMRs and milestones are presented here:

Study 1: A Randomized, Assessor-Blind, Multi-center, Dose-Ranging Study Comparing the Safety and Efficacy of Pre-mixed Oral Solution Formulation versus Active comparator in Children Aged 9 Years to Less than 17 Years

- Protocol Submission: No later than December 2018
- Study Completion: No later than December 2022
- Study Submission: No later than June 2023

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Study 2: A Randomized, Assessor-Blind, Multi-center, Dose-Ranging Study Comparing the Safety and Efficacy of Pre-mixed Oral Solution Formulation versus Active Comparator in Children Aged 2 Years to Less Than 9 Years

- Protocol Submission: No later than December 2019
- Study Completion: No later than December 2023
- Study Submission: No later than June 2024

Study 3: A Randomized, Assessor-Blind, Multi-center, Dose-Ranging Study Comparing the Safety and Efficacy of Pre-mixed Oral Solution Formulation versus Active Comparator in Children Aged 12 months to Less Than 2 Years

- Protocol Submission: No later than December 2021
- Study Completion: No later than December 2025
- Study Submission: No later than June 2026

13 Appendices

13.1. References

See footnotes

13.2. Financial Disclosure

This section is not applicable, because no new clinical trials were conducted in support of this 505(b)(2) NDA for Clenpiq Oral Solution. The Applicant relied upon the safety and efficacy findings for the listed drug, Prepopik powder for oral solution [NDA 202535].
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/s/

SANDHYA K APPARAJU
10/25/2017

PREETI VENKATARAMAN
10/25/2017