CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209589Orig1s000

SUMMARY REVIEW
Cross-Discipline Team Leader Review

Date: November 20, 2017
From: Preeti Venkataraman, MD, Clinical lead CDER/OND/ODE3/DGIEP
Subject: Cross-Discipline Team Leader Review
NDA #: NDA 209589
Applicant: Ferring Pharmaceuticals
Date of Submission: January 31, 2017
PDUFA Goal Date: November 30, 2017

Proprietary Name / Established (USAN) names: CLENPIIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution

Dosage forms / Strength: Solution/ Each bottle contains 10 mg of sodium picosulfate, 3.5 mg of magnesium oxide and 12g of anhydrous citric acid in 160 ml of pre-mixed oral solution (ready-to-drink); Two doses, taken either as a split-dose (preferred) or day-before (alternative)

Proposed Indication(s): Cleansing of the colon as a preparation for colonoscopy in adults
Recommendation: Approval

<table>
<thead>
<tr>
<th>Material Reviewed/Consulted</th>
<th>Names of Discipline Reviewers</th>
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<tbody>
<tr>
<td>Clinical Safety</td>
<td>Sandhya Appanju, Ph.D./Preeti Venkataraman, MD</td>
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<tr>
<td>Pharmacology Toxicology Review</td>
<td>Tanul Chakraborti Ph.D./Sushanta Chakder, Ph. D.</td>
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<tr>
<td>DDMAC/OPDP</td>
<td>Xinyuan Zhang, Ph.D./Insook Kim, Ph.D.</td>
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<tr>
<td>OSE/DMEPA</td>
<td>Meeta Patel, Pharm. D.</td>
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<td>OSE/DPV Pharmacovigilance Review</td>
<td>Matt Barlow, RN, BSN/Sarah K. Vee Pharm. D.</td>
</tr>
<tr>
<td>OMP Patient Labeling Review</td>
<td>Lisa Harinstein, Pharm. D.</td>
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<tr>
<td>Division of Pediatric and Maternal Health</td>
<td>Maternal Review: Catherine Roca, MD; Pediatric Review: Melanie Bhatnagar MD</td>
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1 The reader is referred to the primary review documents for more specific details of the application and review conclusions. This memo summarizes selected information from the primary review documents.
Reference ID: 4183876
1. Introduction

On January 31, 2017, Ferring Pharmaceuticals Inc., submitted an original 505(b)(2) new drug application (NDA) for Clenpiq, NDA 209589, based on the listed drug (LD), Prepopik (NDA 202535). Clenpiq is a ready-to-drink, premixed oral solution for cleansing the colon as preparation for colonoscopy in adults, and is proposed to add more convenience to patient administration since it is ready for oral use without needing reconstitution in cold water prior to administration, as is required for Prepopik. Clenpiq relies upon the LD, Prepopik powder for oral solution, for safety and efficacy information. The applicant of this application is also the owner of the approved NDA 202535 for Prepopik, which was approved in July 2012. The drug product, Clenpiq Oral Solution, has the same active ingredients (10mg sodium picosulfate, 3.5g magnesium oxide and 12g anhydrous citric acid), strength, route of administration, dosing regimen and indications as the reference drug, Prepopik powder for oral solution.

Clenpiq is a combination of sodium picosulfate, a stimulant laxative, and magnesium oxide and anhydrous citric acid which form magnesium citrate, an osmotic laxative, indicated for cleansing of the colon as a preparation for colonoscopy in adults. The active pharmaceutical ingredients of Clenpiq consist of 10mg sodium picosulfate, 3.5g magnesium oxide and 12g anhydrous citric acid. Clenpiq oral solution is provided as a cranberry-flavored, colorless to slightly yellow, clear oral solution, and is supplied as two bottles in each carton. It is a ready to drink premixed oral solution that does not need to be diluted prior to administration. One bottle of Clenpiq is equivalent to one dose. The inactive ingredients in the drug product are the following: acesulfame potassium, cranberry flavor, disodium edetate, malic acid, sodium benzoate, sodium hydroxide, sodium metabisulfite, sucralose, and water. The cranberry flavor contains glycercyl triacetate (triacetin), maltodextrin and sodium octenyl succinated starch.

Two doses of Clenpiq are required for a complete preparation for colonoscopy either as a Split-Dose or Day-Before dosing regimen. The preferred method is the “Split-Dose” method and consists of two separate doses: the first dose during the evening before the colonoscopy and the second dose the next day, during the morning prior to the colonoscopy. The alternative method is the “Day Before” method and consists of two separate doses: the first dose during the afternoon or early evening before the colonoscopy and the second dose 6 hours later during the evening before the colonoscopy. Additional fluids must be consumed after every dose of Clenpiq in both dosing regimens.

2. Background

Colonoscopy is used both diagnostically and therapeutically, and permits examination of the rectum, colon, and a portion of the terminal ileum. A successful colonoscopy requires an adequate preparation of the large bowel that facilitates clear visualization of the mucosal surface 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 effectiveness of the bowel preparation is a critical factor related to the safety and diagnostic accuracy of the examination. There are a number of bowel preparations available for cleansing of the colon prior to colonoscopy in adults.

Clenpiq (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution is a stimulant and osmotic laxative. Sodium picosulfate is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM, which acts directly
on the colonic mucosa to stimulate colonic peristalsis. Magnesium oxide and citric acid react to create magnesium citrate in solution, which is an osmotic agent that causes water to be retained within the gastrointestinal tract. The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a purgative effect which, when ingested with additional fluids, produces watery diarrhea.

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 2/01/2016, where FDA 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 applicant on 5/17/2016. 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. Extensive advice was provided during this meeting regarding the justification needed for an adequate biowaiver request, as well as product quality requirements. An initial agreement on the proposed pediatric study plan was communicated to the applicant on 10/28/2016 after FDA review (refer to Section 10 for details). No clinical studies were conducted in support of this NDA. No nonclinical toxicology studies were submitted in this NDA. The applicant relied upon the FDA findings of safety and efficacy for the LD Prepopik (NDA 202535).

A biowaiver for in vivo BA/BE studies under 21 CFR 320.22(b)(3) was granted because the proposed drug product is an oral solution that contains the same active ingredients in the same concentrations as the LD, Prepopik, and adequate justification was provided supporting the relative bioavailability of the proposed drug product to the reference drug to establish a biobridge to the Agency’s finding of safety and efficacy of the LD.

Clenpiq is a combination drug product with the active pharmaceuticals ingredients of sodium picosulfate, magnesium oxide and anhydrous citric acid. FDA has typically interpreted the regulations at 21 CFR 300.50 to require a factorial analysis of proposed combination ingredients that demonstrates that the combination is more effective than each component of the combination alone. Factorial studies may not be necessary or ethical in certain cases, and FDA may exercise its discretion and need not require an applicant to conduct a clinical study with a factorial design if the Agency deems it unnecessary. During the review of the LD Prepopik (NDA 202535), it was determined that DGIEP could rely on literature to support its decision not to require factorial studies\(^2\). This issue with regard to Clenpiq is discussed in Section 11 below.

\(^2\) Cross Discipline Team Leader Review, NDA 209589, Clenpiq Oral Solution

Reference ID: 4183876
3. OPQ

Drug Substance: Clenpiq contains three active ingredients: sodium picosulfate, magnesium oxide, and anhydrous citric acid. It is provided as a cranberry-flavored, colorless to slightly yellow, clear oral solution, and is supplied as two bottles in each carton. The CMC information is provided in DMF (b)(4) for sodium picosulfate, DMF (b)(4) for magnesium oxide, and DMF (b)(4) for citric acid anhydrous. The three referenced DMFs has been found to be adequate by the OPQ reviewers, and they recommended approval of this new drug application from the drug substance perspective.

Drug Product: The drug product composition is listed below. The three active ingredients are the same as in the listed product, Prepopik. Clenpiq includes additional inactive components to achieve the desired stability, and to improve palatability. According to the OPQ review the “Active and inactive ingredients used in the composition of this drug product are all compendial materials, CLENPIQ™ oral solution is filled in bottles enclosed with caps.”

### Quantitative Composition for Clenpiq Oral Solution

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per 160 mL</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Sodium picosulfate</td>
<td>10 mg</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Magnesium oxide</td>
<td>3.5 g</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Anhydrous citric acid</td>
<td>12 g</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Edetate disodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucralose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acesulfame potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium metabisulfite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranberry flavouring.</td>
<td></td>
<td></td>
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<td>(b)(4)</td>
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Clenpiq oral solution is provided as 160mL filled in a (b)(4) bottle closed with a (b)(4) cap. Two 160-mL bottles of drug product are packed into a single carton supplying the drug product solution for the prescribed two-dose regimen in preparation for colonoscopy. Review by OPQ showed that “the results showed that the proposed container closure complies with all USP requirements. Additionally, the container closure was tested for the extractables/leachables according to recommendation in Product Quality Research Institute (PQRI) and USP <1663>. The results from testing of the proposed container closure for extractables/leachables showed no leachables at the levels of any toxicological concerns.”

The OPQ review further states that “the proposed drug product composition includes a greater amount of edetate disodium than amounts approved in any currently marketed drug products”. The applicant submitted relevant publications and a scientific article to show that the proposed amount of edetate disodium should not be of any toxicological concerns. This information has been reviewed by the nonclinical review team and has been found to be adequate to support the proposed drug product composition. *(Refer to Section 8 for the clinical review of safety of edetate disodium).*

As described by the reviewer, “Acesulfame potassium and Sucralose...”
The applicant of this new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, Clenpiq oral solution, at release and throughout the proposed expiration dating period of 18 months. The overall control strategy of this product in terms of raw material controls, specification, container closure system, and stability is acceptable. Therefore, this application is recommended for approval from the drug product perspective with the expiration dating period of 18 months. The applicant has also made post-approval stability commitments that will be reported to the Agency in annual reports. In summary, the Drug Product Reviewer has concluded that “from the drug product perspective, the applicant has submitted sufficient CMC information that illustrates the applicant can routinely manufacture CLENPIQTM Oral Solution with consistent quality from batch to batch with the desired quality attributes. Therefore, from the ONDP standpoint, Dr. Shafiei has recommended the approval of this new drug application.”

Biopharmaceutical review is discussed in section 5.

Process: The applicant has performed adequate risk assessment of each pivotal manufacturing process step that can impact the quality of the final drug product. Based on the understanding of the manufacturing process and the risks associated with each manufacturing step, the applicant has implemented appropriate controls and in-process testing. Dr. Cheng has recommended the approval of this application.

Microbiology: The applicant demonstrates an adequate level of sterility assurance for the manufacturing process, and provided an adequate description of the drug product composition and the container closure system designed to maintain the microbiological quality of the product. The microbiology reviewers concluded ”the submission is recommended for approval from a Microbiology perspective”.

Office of Facility and Process: The reviewers concluded that “There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities and their previous inspection results, history, and relevant experience. “The Office of Process and Facility has made an overall “Acceptable” recommendation regarding the facilities involved in this NDA.

Environmental Assessment
“The request for the categorical exclusion has been reviewed by the Drug Product Reviewer/ATL, Dr. Hamid Shafiei. Dr. Shafiei has found the applicant’s request for categorical exclusion per 21 CFR § 25.31(a) is deemed valid and has granted the categorical exclusion to this new drug application.”

The final OPQ review (dated 11/6/17) recommended the following:

“The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product”.

“All labels/labeling issues have been resolved”.

“The Office of Process and Facility has made an overall “Acceptable” recommendation regarding the facilities involved in this NDA”.

“Therefore, from the OPQ perspective, this NDA is recommended for
The signatory and this reviewer agree with the OPQ recommendations and findings.

4. Nonclinical Pharmacology/Toxicology

In support of nonclinical safety, the applicant submitted the reports of a pharmacology study in rats, an in vitro permeability study, and is cross-referencing Prepopik, NDA 202535, for nonclinical information. The applicant did not submit any nonclinical toxicology study reports in this NDA. A comprehensive review of nonclinical pharmacology, pharmacokinetics, general toxicology, genotoxicity, and reproductive toxicity studies were conducted in the NDA of the reference drug, Prepopik.

In a pharmacology study in Sprague Dawley rats, oral treatment with Prepopik powder for oral solution and Clenpiq (oral solution) showed similar pharmacological (laxative) effects with respect to onset, stool consistency (fecal score) and duration of action. In the above study, the two formulations appeared to be comparable with respect to pharmacological effect.

The results of permeability studies in Caco-2 cells with magnesium, citric acid and sodium picosulfate and BHPM (active metabolite of sodium picosulfate) using three different formulations (unformulated, Clenpiq, and Prepopik) indicated that these compounds have low permeability, and were similar across treatments and tested concentrations.

The exposure levels of all excipients, including malic acid and disodium edetate, were found to be safe at the proposed concentrations used in the Clenpiq formulation. The exposure level of malic acid is justified by its approval in the US as a food additive, and by findings of nonclinical toxicology studies in rats, rabbits, and dogs. The exposure level of disodium edetate is justified by nonclinical toxicology studies from literature in rats. Thus, there are no safety concerns for any excipients in the proposed drug at the proposed levels from a nonclinical perspective. Three impurities have also been qualified to support the proposed impurity specification, does not appear to raise any significant safety concern, and is acceptable. All the leachables identified were also qualified, and did not raise a safety concern. Overall, the reviewers recommended approval.

(See Section 8 for clinical review regarding the differences in disodium EDTA and malic acid concentrations between this product and the currently marketed product)

5. Clinical Pharmacology/Biopharmaceutics

Several differences in inactive ingredients were identified between the proposed formulation as compared to the LD. To support that the differences in formulation would not affect absorption, or systemic or local availability, the applicant submitted a comparative permeability study and a comparative solubility study under relevant physiological pHs. The biopharmaceutics reviewer concluded that the existence of excipients in the proposed drug product didn’t affect the permeability of active ingredients, and that both Clenpiq and Prepopik have comparable permeability in the tested Caco-2 cell systems, regardless of the difference in excipients composition between them. The solubility study indicated that solubility of the test drug product was maintained over the physiological pH range. The clinical pharmacology reviewer also agreed that the studies were acceptable.

In addition, Clenpiq has a higher sodium content and a higher osmolality compared to Prepopik, and these differences were found not to be of concern from the biopharmaceutical/clinical
pharmacology perspective. The safety of the higher sodium content is justified by clinical experience with other marketed bowel preparation products containing higher levels of sodium, by similar level of exposure from within the range of the recommended dietary intake of sodium, and the non-chronic nature of administration via a bowel preparation (at most 1-2 times in a year if the initial bowel preparation is unsuccessful). The safety of the higher osmolality of Clenpiq is justified by similar osmolalities of routinely ingested beverages (e.g., prune juice, white wine). In addition, as described in the product’s medication guide, after drinking either formulation the patient needs to drink five 8-ounce cups of clear liquids. (See Biopharmaceutics review subsection of OPQ review for more detail).

It was also concluded that the existence of the high amount of malic acid would not affect laxative function of the proposed drug product, and would not pose any safety concern. The applicant’s justification on the presence of edetate disodium was also found to be acceptable from the clinical pharmacology perspective.

The applicant requested a biowaiver of BA/BE requirement per 21 CFR 320.22(a) for this drug product. In accordance with 21 CFR 320.22(b)(3) the applicant has provided adequate information to establish a biobridge between the relative bioavailability of the drug product and Agency’s finding of safety and efficacy of the LD, Prepopik. The justification was found acceptable by the biopharmaceutics reviewer and an additional in vivo bioequivalence (BE) bridging study is not needed. No post-marketing requirement (PMR) or post-marketing requirement commitment (PMC) were recommended from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The proposed drug product has the same active ingredient, strength, route of administration, dosing regimen and indication as the LD, Prepopik. The proposed drug product differs from the LD with respect to the dosage form and the inactive ingredients. The safety and efficacy of the proposed drug product is expected to be same as the LD. The applicant did not conduct any clinical trials, and is relying on the safety and efficacy findings from NDA 202535 for Prepopik.

8. Safety

No new clinical trials were conducted in support of this 505 (b)(2) NDA. The applicant cross-referenced NDA 202535 for Prepopik, which was approved by the Agency in July 2012. The clinical safety of Prepopik is well-established in adult patients who require cleansing of the colon as a preparation for colonoscopy.

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 (\textsuperscript{b}(4)), malic acid (\textsuperscript{b}(4)), sodium benzoate (\textsuperscript{b}(w)), sucrose and acetosulfame potassium.
sodium metabisulfite and sodium hydroxide. These excipients were deemed acceptable by the nonclinical reviewer. The differences in the excipients did not expect to affect in vivo performance of the proposed product, and a biowaiver was granted by the biopharmaceutics reviewer. Clenpiq pre-mixed oral solution (160 mL) also has an approximately 3-fold higher osmolality compared to Prepopik powder reconstituted in 5 ounces of water [1269 mOsm/kg vs. 441 mOsm/kg]. The difference in osmolality was also found to be acceptable by the clinical pharmacology reviewers.

The safety implications of the differences in inactive ingredients, specifically malic acid, edetate disodium, sodium content, and osmolality, were investigated by the primary clinical reviewer (see Dr. Sandhya Apparaju’s review dated October 25, 2017 for details). Each of these differences were found to be acceptable from a clinical perspective, and the associated justification for their safety in Clenpiq is summarized below.

1) The concentration of malic acid in Clenpiq oral solution is an accepted additive for daily consumption (e.g., in processed fruit juices, hard candy). The Joint FAO/WHO Expert Committee on Food Additives proposed that no limit should be set for the Acceptable Daily Intake (ADI) of malic acid in humans; however, the committee noted that the utilization in the body of malic acid is not well understood. A limitation of use was recommended by the committee that neither the malic acid should be added to food for very young infants, except for therapeutic purposes. Although the malic acid exposure potential in adults or pediatric patients is higher with Clenpiq than that approved for common fruit/non-alcoholic beverages, Clenpiq would be used at most once or twice in a year prior to colonoscopy, in contrast to long term exposure via food and beverages, and would not be expected to pose a significant safety concern. Nonclinical justification was also submitted by the applicant, and found to be acceptable by the nonclinical reviewers.

2) Clenpiq contains of edetate disodium per bottle. Orally administered edetate disodium salts are not well absorbed (1-5% per published literature), and therefore the calcium chelation potential is estimated to be low, and not expected to cause clinically meaningful hypocalcemia. 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.

3) The sodium content contained in a single dose of Clenpiq oral solution is higher than that contained in a single dose of Prepopik. The exposure level of sodium is justified by clinical experience with other approved bowel preparations that contain higher amounts of sodium than Clenpiq. The sodium content in Clenpiq 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 at most once or twice in a year. Therefore, from a clinical perspective, the sodium content in Clenpiq does not appear to represent a significant safety concern.

4) 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]. However, the high osmolality of the initial dose of Clenpiq pre-mixed oral solution is not anticipated to result in esophageal irritation, as commonly 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. The measured osmolalities after the intake of additional fluids (40 ounces, as five 8-oz glasses) were similar for the approved Prepopik 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 regarding osmolality from a clinical perspective.

The presence and amounts of the above inactive ingredients, as well as the higher sodium content and osmolality, were found to be acceptable from a clinical perspective.

A review of published literature and FAERS database identified several cases of ‘altered consciousness’ as one of the most frequently reported symptoms in cases of hyponatremia. A review of the identified cases suggests a temporal association of neurological events during or following the intake of the 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 proposed drug product is deemed safe for its intended use for cleansing of the colon as a preparation for colonoscopy in adults. Dr. Sandhya Apparaju, the clinical reviewer, recommended the approval of this NDA for the same indication and target population as Prepopik. Overall, it was determined that there was no change in the risk-benefit between Clenpiq and Prepopik, and a risk evaluation and/or mitigation strategy (REMs) was not recommended.

9. Advisory Committee Meeting
An Advisory Committee Meeting was not conducted as the safety profile is similar to that of the approved LD.

10. Pediatrics
The proposed Clenpiq pre-mixed oral solution has the same active components 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. An iPSP for Clenpiq pre-mixed oral solution was agreed upon in an FDA letter to Ferring dated 10/28/2016 [IND 101738]. The applicant owns both the proposed Clenpiq formulation, as well as the LD formulation, Prepopik. Three studies are planned in pediatric patients ≥12 months of age to evaluate the efficacy and safety of the pre-mixed oral solution formulation. The elements of the agreed iPSP for Clenpiq were agreed upon with PeRC on October 11, 2017 for NDA 209589. The Pediatric Review Committee (PeRC) recommended that 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 Clenpiq will be considered fulfilled if the PREA requirements for Prepopik are fulfilled. It should be noted that the study to fulfill the PREA PMR for Prepopik (NDA 202535) in older pediatric patients (9 – 16 years), is complete and under review by the Agency at the time of this writing.

(Refer to Section 13 for list of PREA PMRs)

11. Other Relevant Regulatory Issues
The financial certification/disclosure statement is not applicable to this application, as no clinical studies were conducted. There are no financial disclosure issues.

The LD, Prepopik, under NDA 202535 from Ferring Pharmaceuticals, Inc. has two unexpired US patents listed in the Orange Book:

Reference ID: 4183876
There is no unexpired exclusivity for this product in the Orange Book database.

Justification for reliance on published literature for the Clinical section to address the regulations at 21 CFR 300.50 (fixed combination prescription drug rule) is as follows:

FDA has typically interpreted the regulations at 21 CFR 300.50 to require a factorial analysis of proposed combination ingredients that demonstrates that the combination is more effective than each component of the combination alone. Factorial studies may not be necessary or ethical in certain cases, and FDA may exercise its discretion and need not require an applicant to conduct a clinical study with a factorial design if the Agency deems it unnecessary.

The review division examined literature for evidence regarding the adequacy of each component as single agents and identified literature studies with bisacodyl and magnesium citrate. Sodium picosulfate and bisacodyl are prodrugs that have the same active metabolite. Magnesium oxide and anhydrous citric acid when mixed in water form magnesium citrate.

The Division found that both components to this combination product are cathartics with different mechanisms of action that each have colon cleansing effects. The literature describes the effectiveness of each component for colon cleansing. A full factorial study could not be conducted due to serious ethical concerns because each component as a stand-alone would result in inadequate colon cleansing for colonoscopy.

Based upon this information it is acceptable to proceed with an approval of this product as recommended by the 505(b)(2) committee.

There are no other unresolved relevant regulatory issues.

12. Labeling

Proprietary Name:
The Office of Medication Error Prevention and Analysis (DMEPA) determined that the proposed proprietary name Clenpiq is acceptable. The reader is referred to the Proprietary Name review by Matthew Barlow, RN, BSN, dated June 6, 2017.

Specific Labeling Issues:
The proposed PI and PPI for Clenpiq Oral Solution is substantially similar to the LD, Prepopik (NDA 202535). In addition to primary review disciplines, the labeling was also reviewed by Division of Pediatric and Maternal Health (DPMH), Division of Medication Error Prevention and Analysis (DMEPA), Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP). Their comments and recommendations have been incorporated into the labeling recommendations for Prescribing Information, Medication Guide, Instructions For Use, and Carton/Container labeling to the applicant. For final labeling agreements, the reader is referred to the approved product label. The key changes and recommended changes to the labeling are summarized below.

Highlights
- Information was added to include dosage and administration instructions for patients

Reference ID: 4183876
taking certain concomitant medications.

• “If taking tetracycline or fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, or penicillamine, take these medications at least 2 hours before and not less than 6 hours after administration of CLENPIQ. (2.1, 7.3)”

Section 7.1

(a general statement was retained, with cross-reference to examples already stated in Section 5 of the labeling).

Section 8.1

• “Pregnancy” was revised to include the “Risk Summary,” and “Data” sections, consistent with the Pregnancy and Lactation Labeling Rule (PLLAR) format.

Section 8.2

• “Lactation” subsection of labeling was revised to include the “Risk Summary”, consistent with the Pregnancy and Lactation Labeling Rule (PLLAR) format.

Section 10

• Specific symptoms of overdosage and instructions to prescribers in the event of overdosage were added.

“Overdosage of more than the recommended dose of CLENPIQ may lead to severe electrolyte disturbances, as well as dehydration and hypovolemia, with signs and symptoms of these disturbances [see Warnings and Precautions (5.1)]. Monitor for fluid and electrolyte disturbances and treat symptomatically.”

Section 17

• The term ‘altered consciousness’ and associated symptoms of confusion, delirium, and loss of consciousness were added.

“Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). Instruct patients:
• To contact their healthcare provider if they develop significant vomiting or signs of dehydration after taking CLENPIQ or if they experience altered consciousness (e.g. confusion, delirium, loss of consciousness) or seizures [see Warnings and Precautions (5.1, 5.2, 5.4)].”

Medication Guide

• A statement was revised to include the term “changes in consciousness” and associated symptoms.

“Contact your healthcare provider right away if after taking CLENPIQ you have severe vomiting, signs of dehydration, changes in consciousness such as feeling confused, delirious or fainting (loss of consciousness) or seizures after taking CLENPIQ.”

13. Recommendations/Risk Benefit Assessment

Regulatory Action: Approval
I am in agreement with the recommendation of the review team to approve Clenpiq Oral Solution for cleansing of the colon as a preparation for colonoscopy in adults. The signatory has reviewed this application as well, and is in agreement with the recommendation for approval.
Risk Benefit Assessment
The overall Benefit-Risk of Clenpiq is similar to that of Prepopik.

No new nonclinical toxicology, clinical safety or efficacy studies were conducted with the proposed drug product in support of this NDA. The NDA for the proposed drug cross-referenced safety and efficacy information for the LD, Prepopik, approved in July 2012. The quality reviewers concluded that the applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The applicant has provided adequate information to establish a biobridge between the relative bioavailability of the drug product and Agency’s finding of safety and efficacy of the LD, Prepopik. Several differences between the proposed and LD product were noted, including content of malic acid, content of edetate disodium, sodium content, and osmolality. The nonclinical, clinical pharmacological, and clinical review of these differences did not identify any significant safety concerns. A safety update revealed that symptoms of altered consciousness were noted to be a frequently reported symptom of hyponatremia. Therefore, additional wording was added to labeling in Section 17 Patient Counseling and the Medication Guide.

Based on the data provided, I agree that Clenpiq oral solution should be approved and that the benefits outweigh the risks associated with the use of this product.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments
No FDAAA Safety PMRs are needed.

The following PREA PMRs will be issued with the approval of Clenpiq (NDA 209589):

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

/s/

PREETI VENKATARAMAN
11/20/2017

JOYCE A KORVICK
11/20/2017