CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209589Orig1s000

NON-CLINICAL REVIEW(S)
PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

<table>
<thead>
<tr>
<th>Application number:</th>
<th>209589</th>
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<tr>
<td>Supporting document/s:</td>
<td>001</td>
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<tr>
<td>Applicant’s letter date:</td>
<td>January 31, 2017</td>
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<td>CDER stamp date:</td>
<td>January 31, 2017</td>
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<tr>
<td>Product:</td>
<td>Clenpiq™ (Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid) Oral Solution</td>
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<td>Indication:</td>
<td>Cleansing of colon as a preparation for colonoscopy in adults</td>
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<td>Applicant:</td>
<td>Ferring Pharmaceuticals, Inc.</td>
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<td>Review Division:</td>
<td>DGIEP</td>
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</table>

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1 Executive Summary

1.1 Introduction
Clenpiq is a bowel preparation product containing the same active ingredients (sodium picosulfate, magnesium oxide, and anhydrous citric acid) as Prepopik® (NDA 202535, Ferring Pharmaceuticals, Inc.) powder for oral solution. The Applicant has developed Clenpiq as a ready-to-drink, pre-mixed oral solution dosage form to eliminate the mixing step, resulting in more convenience to patients.

1.2 Brief Discussion of Nonclinical Findings
The Applicant did not submit any toxicology study report in this submission. However, the Applicant submitted the reports of a pharmacology study and an in vitro permeability study and referred to NDA 202535 for nonclinical information. Please refer to the pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

In a pharmacology study in Sprague Dawley rats, oral treatment with Prepopik powder for oral solution or Clenpiq (oral solution) at 2000 mg/kg BID showed similar pharmacological (laxative) effects with respect to onset, stool consistency (fecal score) and duration of action. In this study, two formulations appeared to be comparable with respect to the 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.

1.3 Recommendations

1.3.1 Approvability
There are no nonclinical approvability issues.

1.3.2 Additional Non Clinical Recommendations
None

1.3.3 Labeling
Nonclinical sections of the proposed draft labeling of CLENPIQ™ conforms to the content and format of labeling for human prescription drug and biological products under 21CFR 201.57. However, the following revisions are recommended.

8.1 Pregnancy

Applicant’s Version:
8.1 Pregnancy

Animal Data

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

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

13. Nonclinical Toxicology
Applicant’s Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with CLENPIQ.

Evaluation: In the second paragraph, multiples of human exposure data was revised based on body surface area calculation.

Recommended Version:


Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with CLENPIQ.

Sodium picosulfate was not mutagenic in the Ames test, the mouse lymphoma assay and the mouse bone marrow micronucleus test.

In an oral fertility study in rats, sodium picosulfate, magnesium oxide, and anhydrous citric acid did not cause any significant adverse effect on male or female fertility up to a maximum dose of 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on body surface area).

2 Drug Information

2.1 Drug

The following is incorporated below from the pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

CAS Registry Number:

Sodium Picosulfate: 10040-45-6
Magnesium Oxide: 1309-48-4
Citric Acid: 77-92-9

Generic Name: Sodium picosulfate, Magnesium oxide, Citric acid

Code Name: N/A
Chemical Name:

Sodium Picosulfate: 4,4’-[(pyridin-2-yl)methylene]diphenyl bis(sodium sulphate) monohydrate
Magnesium Oxide: Magnesium oxide
Citric Acid: 1,2,3-propanetricarboxylic acid, 2-hydroxy

Molecular Formula/Molecular Weight:

Sodium picosulfate: C_{18}H_{13}NNa_{2}O_{6}S_{2}/499.4
Magnesium Oxide: MgO/40.31
Citric acid: C_{6}H_{8}O_{7}/192.14

Structure:

**Sodium picosulfate:**

![Sodium Picosulfate Structure](image)

**Magnesium oxide:** Mg=O

**Citric acid:**

![Citric Acid Structure](image)

Pharmacologic Class: Stimulant laxative (sodium picosulfate)/osmotic laxative (magnesium citrate)
2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 101738 (PicoPrep, Ferring Pharmaceuticals, Inc.)
- NDA 202535 (Prepopik®, Ferring Pharmaceuticals, Inc.)

2.3 Drug Formulation

The Drug Product (DP) is a colorless to slightly yellow clear solution. The DP contains 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid. The following table (from page 1 of Section 3.2.P.1 of the NDA) shows the composition of the DP.

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per 160 mL</th>
<th>Function</th>
<th>Quality standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium picosulfate</td>
<td>10 mg</td>
<td>Active ingredient</td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Magnesium oxide</td>
<td>3.5 g</td>
<td>Active ingredient</td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Anhydrous citric acid</td>
<td>12 g</td>
<td>Active ingredient</td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Edetate disodium</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Malic acid</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Sucralose</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Acetosulphite potassium</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Sodium metabisulfite</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
<tr>
<td>Cranberry flavouring,</td>
<td></td>
<td>Flavouring agent</td>
<td>In-house specification</td>
</tr>
<tr>
<td>water</td>
<td></td>
<td></td>
<td>USP-NF curr. ed.</td>
</tr>
</tbody>
</table>

2.4 Comments on Novel Excipients

The amounts of all excipients used in the DP are within the Inactive Ingredients Database (IID) values, except malic acid and cranberry flavor. The Applicant has referred to DMF# for cranberry flavor. This DMF was found to be adequate for the use of the flavor for Prepopik oral solution (chemistry review dated August 20, 2014 by Yubing Tang, PhD). Sucralose is used at a concentration of which is acceptable as higher amounts of sucralose have been used in other approved bowel preparation products.

Malic Acid: The Applicant has provided safety assessment of malic acid (Report No. 2720). Malic acid is present in most fruits and many vegetables. Malic acid is used in the DP Two doses of Clenpiq are recommended within a 24-hour period. Each dose contains of malic acid per which amounts to which is approximately Malic acid is approved for use as a food additive in the USA.
Acceptable Daily Intake (ADI) has been set for malic acid [The Joint FAO-WHO Expert Committee on Food Additives (JECFA), 1967]. Acute oral toxicity of malic acid is low (LD₅₀ ~ 3 g/kg in rats and rabbits). Malic acid was not mutagenic in the Ames test and chromosome aberration assay [Fiume Z, 2001, Final Report on the Safety Assessment of Malic Acid and Sodium Malate, Int J Toxicol, 20(Suppl. 1):47-55]. In a 104-week oral dietary toxicity study [Fiume Z, 2001, Final Report on the Safety Assessment of Malic Acid and Sodium Malate, Int J Toxicol, 20(Suppl. 1):47-55] with malic acid in rats and dogs, the No Observed Adverse Effect Level (NOAEL) was considered as 50,000 ppm or 5% (approximately 2500 and 1250 mg/kg/day for rat and dog, respectively), the highest tested dose, in both species. The NOAEL of 2500 mg/kg/day in rats and 1250 mg/kg/day in dogs offer adequate (about 9 and 5 times, respectively) margin of safety for the ingestion 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. In addition, the drug is recommended as split-dose (first dose during the evening before the day of the colonoscopy and the second dose during the morning on the day of the colonoscopy) for the preparation of colonoscopy. Overall, the presence of malic acid in 160 mL of Clenpiq oral solution does not appear to raise any safety concern and is acceptable.

Edetate Disodium (Disodium EDTA):

Disodium Ethylenediaminetetraacetic Acid (EDTA, CAS No: 139-33-3) is added as a component in Clenpiq oral solution at a concentration of 3.44%. Two doses are administered within a 24-hour period as a “Split-Dose” dosing regimen. Each dose contains 29.8 mg of disodium EDTA. In rats, disodium EDTA was poorly absorbed and rapidly excreted from the gastrointestinal (GI) tract following oral administration. Disodium EDTA has a low order of acute toxicity. In Wistar rats, oral LD₅₀ of disodium EDTA was reported to be ~3.7 g/kg for both sexes (Lanigan RS and Yamarik TA, 2002, Final Report on the Safety Assessment of EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, Disodium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDETA, and Trisodium HEDTA, Int J Toxicol, 21 (Suppl 2):95-142). In a subchronic toxicity study in rats, animals were fed a diet containing 0, 0.5, 1.0 and 5% (equivalent to 0, 250, 500, and 2500 mg/kg/day, respectively) of disodium EDTA for 90 days (Heimbach J et al., 2000, Safety Assessment of Iron EDTA [Sodium Iron (Fe³⁺) Ethylenediaminetetraacetic Acid]: Summary of Toxicological, Fortification and Exposure Data, Food Chem Toxicol, 38:99-111). There were no significant treatment related adverse effects other than diarrhea and reduced food consumption at the high dose. Based on these, the highest tested dose of 2500 mg/kg/day was considered a well-tolerated dose. In addition, EDTA compounds are not considered mutagenic or genotoxic under conditions that do not deplete essential trace elements required for normal cell function (Heimbach J et al., 2000, Safety Assessment of Iron EDTA [Sodium Iron (Fe³⁺) Ethylenediaminetetraacetic Acid]: Summary of Toxicological, Fortification and Exposure Data, Food Chem Toxicol, 38:99-111). Overall, the 2500 mg/kg/day dose used in the above subchronic toxicity study in rats provides approximately 33fold margin of safety for the disodium EDTA exposure of a 3-year-old child from Clenpiq. Therefore, the level of
of disodium EDTA per dose (160 mL) of Clenpiq does not appear to raise any significant safety concern and is acceptable.

2.5 Comments on Impurities/Degradants of Concern

Drug products impurities are shown in the following table (from page 2 of 3.2.P.5.5 of the NDA).

The acceptance criteria for the impurities were set based on the Qualification Threshold (QT) of \[ \text{(b)(4)} \] per the ICH Q3B (R2) guidance. Per ICH Q3B (R2), “a higher qualification threshold can be appropriate for individual new drug products when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, and clinical considerations)”. Per the above guidance, a QT of \[ \text{(b)(4)} \] or \[ \text{(b)(4)} \] Total Daily Intake (TDI), whichever is lower, applies for drugs with maximum daily dose of \[ \text{(b)(4)} \]. Based on the maximum daily dose of \[ \text{(b)(4)} \] of \[ \text{(b)(4)} \] the QT was determined to be \[ \text{(b)(4)} \]. However, as stated above, higher qualification thresholds may be appropriate when the level of concern for safety is less than usual. A \[ \text{(b)(4)} \] times QT of \[ \text{(b)(4)} \], i.e. \[ \text{(b)(4)} \] was set as the Drug Product (DP) is intended to be administered for 1-day treatment only for the preparation for colonoscopy. The proposed QT of \[ \text{(b)(4)} \] for the impurities in the drug product appears to be justified and is acceptable.

All impurities, with the exception of the specified impurities \[ \text{(b)(4)} \] remained at \[ \text{(b)(4)} \] for the duration of stability studies conducted at the proposed shelf-life storage conditions as shown in the table below (from page 3 of 23.2.P.5.5 of the submission).
Container Closure System

The Container Closure System (CCS) used for sodium picosulfate, magnesium oxide, and anhydrous citric acid oral solution is shown in the table below (from page 2 of 3.2.P.7 of the SDN 001 dated January 31, 2017). The drug product is filled in bottles, and closed with caps (PP 28).

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
2.6 Proposed Clinical Population and Dosing Regimen

Clenpiq is indicated for cleansing of the colon as a preparation for colonoscopy in adults.

Clenpiq is supplied as an oral solution. One bottle of Clenpiq is equivalent to one dose.

- Two dosing regimens, each requires two separate dosing times as follows:
- “Split-Dose” method is preferred method
  - First Dose: during evening before the colonoscopy
  - Second Dose: next day, during the morning prior to the colonoscopy
- “Day-Before” method is alternative method if “Split-Dose” is not appropriate
  - First Dose: during afternoon or early evening before the colonoscopy
  - Second Dose: 6 hours later during evening before colonoscopy
2.7 Regulatory Background

- Type C meeting was held on February 1, 2016 (meeting minutes dated February 3, 2016)
- Type B pre-NDA meeting was held on May 17, 2016 (meeting minutes dated May 25, 2016)

3 Studies Submitted

3.1 Studies Reviewed

- Pharmacology
- In vitro permeability study of Mg\(^{++}\), citrate, sodium picosulfate, and bisacodyl related compound a in the presence and absence of excipients (Report No. 17FERRNJP1)

3.2 Studies Not Reviewed

The following method validation studies are not reviewed:

- Evaluation of Historical Variability of Minoxidil Apparent Permeability Across Caco-2 Cell Monolayers (Report No. 16ASLP_Minoxidil Creteria)
- Revalidation of the Caco-2 System for BCS In Vitro Permeability Studies (Report No. 6ASLPBCSval)
- Tolerability of Caco-2 Cell Monolayers to Test Formulations (Report No. 15FERRNJP1R11)
- Tolerability and Permeability in Caco-2 Cell Monolayer System of Test Articles, Formulated and Unformulated (Report No. 15FERRNJP1R8)

3.3 Previous Reviews Referenced

- Pharmacology of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

4 Pharmacology

4.1 Primary Pharmacology

Comparison of Two Different Formulations in a 1-Day Dose Cross-Over Study in Rats and 5-Day Oral Toxicity Study of Sodium Picosulfate, Magnesium Oxide, Anhydrous Citric Acid Oral Solution in Rats (Report No. 77647)

**Methods**: This study was conducted in two phases. The aim of phase 1 (1-day cross-over) was to compare the pharmacological effects of two different formulations of Prepopik\(^{(b,4)}\) in Sprague Dawley rats. The formulations were administered by oral gavage twice on one day, 8 hours apart, for 5 consecutive days. In Phase 2, the toxicity of an impurity-spiked oral solution was
compared to the toxicity of the unspiked oral solution. The structure of the impurity is shown below (from page 13 of the report).

The following tables (from page 17-18 of the report) show the study designs for phase 1 and phase 2.
**Table 1  Treatment schedule – Phase 1 (first treatment - Day 1)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Formulation</th>
<th>Dose (mg/kg BID*)</th>
<th>Dose concentration (mg/mL)</th>
<th>Animal Nos</th>
<th>Colour code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prepopik®&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2000</td>
<td>100</td>
<td>1-5</td>
<td>6-10</td>
</tr>
<tr>
<td>2</td>
<td>Sodium Picosulfate, Magnesium Oxide, Anhydrous Citric Acid Oral Solution</td>
<td>2000</td>
<td>100</td>
<td>11-15</td>
<td>16-20</td>
</tr>
</tbody>
</table>

<sup>6</sup> Bis in die
- The dose was given by oral gavage according to the most recent body weight data.
- The dose was given twice on one day with 8 hours (±30 min) between the two doses (total daily dose 4000 mg/kg).
- Dose volume was 20 mL/kg body weight.
- The first day of treatment was designated Day 1.
- After dosing, the rats were placed in clean cages, see 3.6.

**Table 2  Treatment schedule – Phase 1 (second treatment – Day 8)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Formulation</th>
<th>Dose (mg/kg BID*)</th>
<th>Dose concentration (mg/mL)</th>
<th>Animal Nos</th>
<th>Colour code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium Picosulfate, Magnesium Oxide, Anhydrous Citric Acid Oral Solution</td>
<td>2000</td>
<td>100</td>
<td>1-5</td>
<td>6-10</td>
</tr>
<tr>
<td>2</td>
<td>Prepopik®&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2000</td>
<td>100</td>
<td>11-15</td>
<td>16-20</td>
</tr>
</tbody>
</table>

<sup>6</sup> Bis in die
- The dose was given by oral gavage according to the most recent body weight data.
- The dose was given twice on one day with 8 hours (±30 min) between the two doses (total daily dose 4000 mg/kg).
- Dose volume was 20 mL/kg body weight.
- After dosing, the rats were placed in clean cages, see 3.6.
Clinical signs, body weight and food consumption were measured in phase 1. In phase 2, in addition to the above parameters, specified tissues (small intestine, large intestine, mesenteric lymph node, esophagus, stomach and tongue) were examined for macroscopy and microscopy.

Results:

Phase 1: The results of the phase 1 study indicated that pharmacological (laxative) effects of Prepopik® and sodium picosulfate, magnesium oxide, anhydrous citric acid oral solution (Glunbid) were similar. The time of onset of action (pharmacological effect) for both the formulations on Day 1 and Day 5 was 6 to 8 hours postdose, with scores between 3 (soft feces, still with shape) and 5 (watery feces). A few sporadic scores of 3 were observed from 2 to 5 hours postdose, and one score of 4 (soft feces, no shape) for Prepopik® was observed at 5 hours postdose. The effect was observed at 1-2 hours postdose after the second dose. Normal feces were observed at 8 hours after the second dose for both formulations. Clinical signs for all animals treated with sodium picosulfate, magnesium oxide, anhydrous citric acid oral solution (4000 mg/kg/day) or Prepopik® (4000 mg/kg/day) included minimal to moderate piloerection, decreased activity and dehydration. These clinical signs were considered related to the test articles. Animal No. 6 (female, 500 mg/kg BID, unspiked) was found dead on Day 8 as shown in the table above. Macroscopic evaluation of this animal revealed small reddened foci in the glandular mucosa of the stomach. The cause of death was not identified and was the death was considered incidental.

Phase 2: Treatment (both formulations) related clinical signs included minimal to moderate piloerection, and decreased activity. There were no significant treatment related effects on body weight or food consumption. At necropsy, small reddened foci were described in the glandular mucosa of the stomach of animal number 6 (found
dead) and animal number 11. There were no significant treatment related histopathology findings. Due to clinical signs observed in Phase 1 at [_____] mg/kg BID, the dose was reduced in Phase 2 to [_____] BID. Only minor differences between the impurity-spiked and the unspiked version of sodium picosulfate, magnesium oxide, anhydrous citric acid oral solution were observed, e.g. decreased activity was more pronounced in both sexes in the group treated with the spiked test item. Overall, there were no significant differences in toxicity profiles between spiked and unspiked group that could be contributed by the impurity.

Overall, similar pharmacological effects (laxative) were observed following oral administrations of Prepopik® powder or Clenpiq oral solution in rats at [_____] BID. Based on the results of this study, two formulations appeared to be comparable with respect to pharmacological effect. Oral treatment of rats with sodium picosulfate, magnesium oxide, anhydrous citric acid oral solution either unspiked or spiked with the impurity at a concentration of [_____] for 5 days were well-tolerated and revealed no significant difference between the treatments that could be contributed to the impurity.

4.2 Secondary Pharmacology
None

4.3 Safety Pharmacology
None

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

In Vitro Permeability Study of Mg++, Citrate, Sodium Picosulfate, and Bisacodyl Related Compound in the Presence and Absence of Excipients (17FERRNJP1)

Methods: The objective of this study was to examine the in vitro permeability of Mg++, citric acid, sodium picosulfate, and bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM, a metabolite of sodium picosulfate) in two different formulations and without excipients (unformulated) using Caco-2 cell monolayers. Atenolol and minoxidil were used as internal reference compounds. The apical-to-basolateral (A-to-B) in vitro permeability of Mg++, citric acid, sodium picosulfate, and BHPM across Caco-2 cell monolayers was determined with 3 dilutions of Formulation 1 (Prepopik® oral solution) and Formulation 2 (Prepopik®) including the unformulated. The concentrations tested in the permeability assay were equivalent to 1%, 2%, 10%, 15%, and 20% of the clinical dose of each of the formulations for BHPM, or 10%, 15%, and 20% for magnesium oxide (MgO), citric acid, and sodium picosulfate. Samples were analyzed by LC-MS/MS.
**Results:** The results of the permeability studies in Caco-2 cells with magnesium, citric acid and picosulfate and BHPM using three different formulations (unformulated, Clenpiq and Prepopik) indicated that these compounds have low permeability and the A-to-B $P_{app}$ (apparent permeability coefficient) of all four analytes was similar across treatments and across the tested concentrations.

5.2 **Toxicokinetics**

Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

6 **General Toxicology**

6.1 **Single-Dose Toxicity**

None

6.2 **Repeat-Dose Toxicity**

The Applicant did not submit any study report.

7 **Genetic Toxicology**

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

7.2 *In Vitro* Assays in Mammalian Cells

Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

7.4 **Other Genetic Toxicity Studies**

None

8 **Carcinogenicity**

The Applicant has not conducted any carcinogenicity study with Clenpiq. Carcinogenicity studies are not required for the marketing of colonoscopy preparations.
9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development
Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

9.2 Embryonic Fetal Development
Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

9.3 Prenatal and Postnatal Development
Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

10 Special Toxicology Studies
Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

11 Integrated Summary and Safety Evaluation
In a pharmacology study in Sprague Dawley rats, oral treatment with Prepopik powder for oral solution and Clenpiq (oral solution) at 2000 mg/kg BID showed similar pharmacological (laxative) effects with respect to onset, stool consistency (fecal score) and duration of action. In the above study, 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.

The Applicant did not submit the report of any toxicology study and referred to NDA 202535 (Prepopik) for nonclinical information. Please refer to pharmacology review of NDA 202535 dated May 14, 2012 by Tamal Chakraborti, PhD.

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.

12 Appendix/Attachments
None
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/s/

TAMAL K CHAKRABORTI
10/13/2017

SUSHANTA K CHAKDER
10/13/2017