DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS

Combined (CDTL and Signatory) Clinical Review

NDA:	209589
eDR Link	\\CDSESUB1\evsprod\NDA209589\0028
Sponsor or Investigator:	Ferring Pharmaceutcials
Drug:	Clenpiq
Drug Class:	Cathartic/Laxative (Bowel Preparation)
Dose(s) & Units:	Each dose contains 10mg sodium picosulfate, 3.5g magnesium oxide, 12g anhydrous citric acid in 160ml solution
Route & Frequency:	Oral for single administration prior to colonoscopy
Proposed Indication:	Cleansing of the colon prior to colonoscopy
Date Received:	11/2/18
PDUFA Goal Date:	9/2/19
Date review Completed:	7/31/19
Team Leader:	Tara Altepeter, MD
Project Manager:	Cheronda Cherry-France
Division Signatory:	Jessica J. Lee, MD, Associate Director, DGIEP

Recommended Regulatory Action: Approval

Brief Memo:

Clenpiq (sodium picosulfate, magnesium oxide, anhydrous citric acid) Oral Solution was approved for the cleansing of the colon prior to colonoscopy in adults on November 28, 2017. The application was approved as a 505(b)(2) new drug application based on reliance on the Agency's previous findings of safety and efficacy for the listed drug (LD) Prepopik (NDA202535).

Clenpiq is a ready to drink, pre-mixed oral solution for cleasing the colon, which does not require reconstitution prior to ingestion. Clenpiq has the same active ingredients, strength, route of administration, dosing regimen, and indications as the LD, Prepopik. No new clinical trials were conducted in support of the 505(b)(2) application for Clenpiq. The differences between Clenpiq and Prepopik were minor, and included minor differences in the amount of inactive ingredients (malic acid, edetate disodium), the sodium content, and osmolalilty. These differences were determined to be acceptable and were not found to present new or unacceptable safety risks, as detailed in the CDTL review of NDA209589 by Dr. Preeti Venkataraman (dated 11/20/2017).

At the time of approval of Clenpiq, the applicant was issued deferred post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) for the following:

- 3252-1 A randomized, assessor-blind, multicenter, dose-ranging study comparing the safety and efficacy of clenpiq pre-mixed oral solution formulation vs active comparator in children aged 9 years to less than 17 years of age.
- 3252-2 A randomized, assessor-blind, multicenter study comparing the safety and efficacy of clenpiq pre-mixed oral solution formalation vs active comparator in children aged 2 years to less than 9 years of age

- 3252-3 A randomized, assessor-blind, multicenter study comparing the safety and efficacy of clenpiq pre-mixed oral solution formalation vs active comparator in children aged 12 months to less than 2 years of age

These study requirements are identical to the studies that were issued under PREA for Prepopik, with the intention that if the sponsor completes these studies with Prepopik, the results would also be adequate to satisfy the PREA requirements for Clenpiq. This approach was agreed to by the Pediatric Review Committee (PeRC) (see minutes dated 12/1/17) during the review cycle for the initial NDA for Clenpiq.

Study 1902-1 (PMR issued for Prepopik) for the study of pediatric patients 9 years to 16 years of age was reviewed under NDA202535, supplement 5 (approved on 8/15/18) and resulted in expansion of the indication for Prepopik to include patients down to 9 years of age.

The sponsor is propsing to update the Clenpiq label with the same changes that were added to the Prepopik label at the time that supplement was approved to expand the indication down to 9 years of age.

Key Review Issues:
The review team noted that the osmolality of Clenpiq is approximately 3 times higher than a reconstituted dose of Prepopik. High osmolality is the main mechanism by which the drug product causes catharsis, and thus differential osmolality could, in theory, result in more diarrhea and/or greater risk of dehydration. The review team considered whether or not this could pose a differential safety concern for pediatric patients, if patients failed to take the required clear liquids after ingestion of a dose of clenpiq. Additional information was requested from the applicant to address this concern (information request sent 1/25/19) and response was received on 2/25/19, and is summarized below.

1) Higher osmolality of Clenpiq dose (1269 mOsm/kg) compared with Prepopik (reconstituted dose) (441 mOsm/kg) is noted. (b) (4)

These contributors are mostly absorbed/metabolized prior to the contents of the GI lumen reaching the colon as follows:

- (b) (4)
-

2) The main osmotically active ingredient contributing to the effect of the drug(s) is (b) (4), which remains similar between the two formulations and the concentration of which would not be impacted by the mechanisms described above.

3) Dilution of the ingested drug product by GI secretions (GI and small intestinal secretions) will result in similar osmolality of the drug product by the time it reaches the colonic lumen, the site of action. This assertion is supported by data and simulations that were submitted and reviewed by FDA in the initial biowaiver request (Request for Biowaiver dated 1/29/2017, and Q-Report 13433 dated 1/30/2017).

Table 1 compares anticipated osmolality of Prepopik and Clenpiq after dilution with gastric and small bowel secretions (before any additional clear liquid intake), as well as after ingestion of additional clear liquids as instructed during bowel preparation. It is notable that even prior to beginning dilution with additional exogenous clear liquids (see column titled 100ml SIF below), the effect of gastrointestinal secretions minimizes the difference in osmolality of the two products. Further, after ingestion of only the first 8 oz of clear liquids (colum titled 1) osmolalities are fairly comparable. These data support the applicant's assertion that the differences in osmolality present in the [redacted] (b) (4) prior to ingestion are minimized by a combination of factors, including absorption/metabolism of inactive ingredients contributing to the difference in osmolality, dilution by gastrointestinal secretions, and finally, ingestion of required additional clear liquids. Even without the additional clear liquids, the difference is much less pronounced by the time the ingested drug product reaches the colon. Further, it is noted that the osmolality of some of the sample clear liquids (i.e. white grape juice) is almost as high as that of Clenpiq.

Table 1: Osmolality (mOsm/kg) of PREPOPIK and CIENPIQ after sequential dulation of gastrointestinal secretions and clear liquids of varying osmolality

Solution	Osmolality (mOsm) N=3							
	Neat	50 mL SGF	100mL SIF	8 ounce glasses				
				1	2	3	4	5
Low Osmolality Liquids								
Jell-O (82 mOsm)								
PREPOPIK®	441	385	300	176	146	134	125	122
CLENPIQ™	1269	1014	730	376	289	274	249	190
Gatorade (139 mOsm)								
PREPOPIK®	441	385	300	213	185	174	164	160
CLENPIQ™	1269	1014	730	389	302	256	230	215
Tap Water (18 mOsm)								
PREPOPIK®	441	385	300	139	88	71	59	51
CLENPIQ™	1269	1014	730	316	205	154	126	110
High Osmolalty Liquids								
White Grape Juice (1082 mOsm)								
PREPOPIK®	441	385	300	765	876	939	968	1015
CLENPIQ™	1269	1014	730	950	1000	1024	1044	1049
Cranberry Juice (563 mOsm)								
PREPOPIK®	441	385	300	478	513	532	541	551
CLENPIQ™	1269	1014	730	654	626	613	603	601
Apple Juice (765 mOsm)								
PREPOPIK®	441	385	300	574	644	682	700	714
CLENPIQ™	1269	1014	730	764	774	776	779	779
Beef Broth (mOsm)								
PREPOPIK®	441	385	300	344	353	356	360	365
CLENPIQ™	1269	1014	730	522	458	431	413	406

SGF = Simulated Gastric Fluid without pepsin (2% w/v sodium chloride in 0.7% v/v hydrochloric acid
SIF = Simulated Intestinal Fluid without pancreatin (potassium dihydrogen phosphate, sodium hydroxide)
Jell-O (Lemon lime Jell-O sugar free), Gatorade (G2 Glacier Freeze), White grape juice (Welch's 100% crisp), Apple juice (Welch's pourable concentrate – diluted), White cranberry juice (Ocean Spray).

Source: sponsor's request for biowaiver (Table 11 of submission dated 1/29/17, pg 24/33)

Thus, it appears reasonable to conclude that the differential osmolality of a dose of Clenpiq, as compared to a reconstituted dose of Prepopik, is unlikely to pose a differential safety concern in pediatrics, irrespective of the ability of the child to ingest additional clear liquids per the Dosage and Adminstration. Ability of pediatric patients to comply with recommendations for additional fluid intake remains an important issue that may affect efficacy and/or safety, and will be addressed in each of the subsequently planned pediatric clinical trials utilizing Prepopik/Clenpiq. The sponsor was advised to include a diary for patients/parents to document the type and volume of clear liquids taken after each dose, so that

compliance with the total volume of clear liquid recommended after each dose of Clenpiq is captured and can be analyzed.

Key Labeling Changes:

- Expansion of the indication to include patients down to 9 years of age
- Addition of common (>5%) adverse reactions of nausea, vomiting and abdominal pain for patients 9 to 16 years of age
- Addition of information to the warnings and precautions regarding the occurrence of orthostatic hypotension
- Inclusion of cases of (b) (4) in section 6.1
- Addition of text to section 8.4 Pediatrics describing the basis of approval for patients 9 years of age and older (reliance upon adult data and a single controlled study in patients 9 to 16 years of age).
- Inclusion of pediatric PK information in section 12.3
- Inclusion of efficacy results for the pediatric trial 1902-1 in section 14

The labeling changes are consistent with those negotiated during the sNDA review of supplement 5 to Prepopik and are acceptable.

Conclusions:

The previously conducted pediatric clinical study 1902-1 (PMR issued for Prepopik) is sufficient to satisfy the requirements of PMR 3252-1 for Clenpiq, given that the products contain the same active ingredients in the same quantities, and a biowaiver for *in vivo* BA/BE studies was granted. No additional studies using the Clenpiq formulation are deemed necessary to support a pediatric approval down to 9 years of age.

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

/s/

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07/31/2019 01:52:27 PM

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07/31/2019 02:00:43 PM