Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 4, 2022
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Product Names:	Prepopik (sodium picosulfate, magnesium oxide, and anhydrous citric acid) Clenpiq (sodium picosulfate, magnesium oxide, and anhydrous citric acid)
Pediatric Labeling Approval Date:	August 15, 2018 (Prepopik) August 8, 2019 (Clenpiq)
Application Type/Number:	NDA 202535 (Prepopik) NDA 209589 (Clenpiq)
Applicant:	Ferring Pharmaceuticals
TTT Record ID:	2022-796

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Prepopik (sodium picosulfate/magnesium oxide/anhydrous citric acid) or Clenpiq (sodium picosulfate/magnesium oxide/anhydrous citric acid) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events associated with Prepopik or Clenpiq in pediatric patients.

Prepopik and Clenpiq consist of 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. Prepopik is supplied as a powder that must be reconstituted with water prior to use whereas Clenpiq is supplied as a ready to drink solution that does not require dilution prior to administration. The applicant for both products is Ferring Pharmaceuticals. This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change for Prepopik on August 15, 2018, and the labeling change for Clenpiq on August 8, 2019, that reflected the products' approval for use in patients 9 years and older. DPV has not previously presented Prepopik or Clenpiq to the Pediatric Advisory Committee.

DPV reviewed all FAERS reports for Prepopik or Clenpiq in the pediatric population (ages 0 through 16 years) for all dates through August 8, 2022. The FAERS search identified three reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to Prepopik or Clenpiq.

DPV will continue to monitor all adverse events associated with the use of Prepopik or Clenpiq.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Prepopik (sodium picosulfate/magnesium oxide/anhydrous citric acid) or Clenpiq (sodium picosulfate/magnesium oxide/anhydrous citric acid) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events associated with Prepopik or Clenpiq in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Prepopik and Clenpiq consist of 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. Prepopik is supplied as a powder that must be reconstituted with water prior to use whereas Clenpiq is supplied as a ready to drink solution that does not require dilution prior to administration. The applicant for both products is Ferring Pharmaceuticals.[1,2]

FDA first approved Prepopik on July 16, 2012. Initially, Prepopik was only approved for adult patients. FDA expanded the Prepopik indication to include pediatric patients aged 9 years and older on August 15, 2018. Safety and efficacy for Prepopik use in patients 9 years and older relied on literature to support the contribution of each component of the combination product.[1,3] Additionally, safety and efficacy was supported by an adequate and well-controlled trial including patients 9-16 years old in whom the observed successes rates were similar to the comparator, polyethylene glycol, in both the 9-12 year old age group (88% and 81%, respectively) and the 13-16 year old age group (81% and 83%, respectively). The alternative dosage studied, Prepopik ½ sachet x 2 doses, did not demonstrate comparable efficacy to the comparator drug in subjects 9-12 years old (50% and 81%, respectively). The risks associated with Prepopik within the pediatric trial were similar to those observed and characterized within the clinical trials in the adult population.[3,4] Marketing for Prepopik has been discontinued in the U.S.[5]

Clenpiq was initially approved by FDA on November 28, 2017, for use in adult patients.[2,6] The indication was expanded to include pediatric patients 9 years and older on August 8, 2019. Results from the Prepopik pediatric studies from the same applicant satisfied the PREA postmarketing requirement for Clenpiq and the indication for Clenpiq was expanded to include pediatric patients aged 9 years and older on August 8, 2019.[6]

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change for Prepopik on August 15, 2018, and the labeling change for Clenpiq on August 8, 2019, that reflected the products' approval for use in patients 9 years and older. DPV has not previously presented Prepopik or Clenpiq to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1,2]

The Prepopik and Clenpiq labelings contain the following safety information excerpted from the Highlights section of the labelings. For further Prepopik or Clenpiq labeling information, please refer to the full prescribing information.

Prepopik:

----------CONTRAINDICATIONS----------

• Severe renal impairment (creatinine clearance less than 30 mL/minute) (4)
• Gastrointestinal (GI) obstruction or ileus (4)
• Bowel perforation (4)
• Toxic colitis or toxic megacolon (4)
• Gastric retention (4)
• Hypersensitivity to any of the ingredients (4)

----------WARNINGS AND PRECAUTIONS----------

• Risk of fluid and electrolyte abnormalities: Encourage adequate hydration, assess concurrent medications, and consider laboratory assessments prior to and after use. (5.1, 5.2, 7.1)
• Cardiac arrhythmias: Consider pre-dose and post-colonoscopy ECGs in patients at increased risk. (5.2)
• Seizures: Use caution in patients with a history of seizures and patients at increased risk of seizure, including medications that lower the seizure threshold. (5.3, 7.1)
• Patients with mild to moderate renal impairment or taking concomitant medications that affect renal function: Use caution, ensure adequate hydration and consider testing. (4, 5.4, 7.1)
• Mucosal ulcerations: Consider potential for mucosal ulcerations when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease. (5.5)
• Suspected GI obstruction or perforation: Rule out diagnosis before administration. (4, 5.6)
• Patients at risk for aspiration: Observe during administration. (5.7)
• Risk of vomiting and other GI complications with ingestion of undissolved powder: Dissolve each packet in 5 ounces of cold water and administered at separate times according to the dosing regimen. (2.3, 2.4, 5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:
• Adults (>1%): nausea, headache and vomiting. (6.1)
• Pediatrics 9 to 16 years (>5%): nausea, vomiting, and abdominal pain. (6.1)

Clenpiq:

----------CONTRAINDICATIONS----------

• Patients with severe reduced renal impairment (creatinine clearance less than 30 mL/minute) (4, 5.3, 8.6)
• Gastrointestinal (GI) obstruction or ileus (4)
• Bowel perforation (4)
• Toxic colitis or toxic megacolon (4)
• Gastric retention (4)
• Hypersensitivity to any of the ingredients in CLENPIQ (4)

----------WARNINGS AND PRECAUTIONS----------

• Risk of fluid and electrolyte abnormalities, arrhythmia, seizures, and renal impairment: encourage adequate hydration, assess concurrent medications, and consider laboratory assessments prior to and after use. (5.1, 5.2, 5.3, 5.4,7.1)
• Use in patients with renal impairment or taking concomitant medications that affect renal function: Use caution, ensure adequate hydration, and consider testing. (4, 5.3, 7.1)
• Mucosal ulcerations: Consider potential for mucosal ulcerations when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease. (5.5)
• Suspected GI obstruction or perforation: Rule out diagnosis before administration. (4, 5.6)
• Patients at risk for aspiration: Observe during administration. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:
• Adults (≥2%): nausea, headache, hypermagnesemia, abdominal pain and dehydration or dizziness. (6.1)
• Pediatrics 9 to 16 years (>5%): nausea, vomiting, and abdominal pain. (6.1)

----------DRUG INTERACTIONS----------

Drugs that increase risks due to fluid and electrolyte changes. (7.1)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table X. FAERS Search Strategy*	
Date of search	August 9, 2022
Time period of search	All reports through August 8, 2022
Search type	RxLogix PV Signal Quick Query
Product terms	Product Active Ingredient: Anhydrous citric acid\magnesium oxide\sodium picosulfate
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

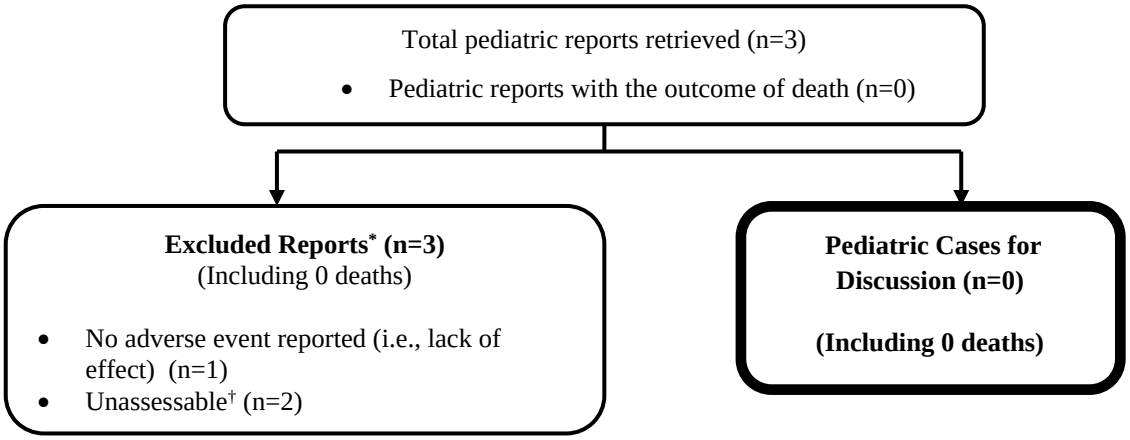
Table 2 presents the number of adult and pediatric FAERS reports through August 8, 2022, with Prepopik or Clenpiq.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through August 8, 2022, With Prepopik or Clenpiq			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	755 (563)	323 (131)	22 (3)
Pediatrics (0 - <17 years)	3 (1)	2 (0)	0 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.			

3.1.2 Selection of Pediatric Cases in FAERS

The FAERS search retrieved three pediatric reports with Prepopik or Clenpiq through August 8, 2022. DPV reviewed the three FAERS reports and excluded all reports from further discussion due to no adverse event being reported (n=1) or being unassessable (n=2). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Prepopik or Clenpiq



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above.
† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for further discussion.

4 DISCUSSION

DPV reviewed all FAERS reports for Prepopik or Clenpiq in the pediatric population (ages 0 through 16 years) for all dates through August 8, 2022. The FAERS search identified three reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to Prepopik or Clenpiq.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Prepopik or Clenpiq at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of Prepopik or Clenpiq.

7 REFERENCES

1. Prepopik (sodium picosulfate, magenssum oxide, and anhydrous citric acid) for oral solution. [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc. August 2018.
2. Clenpiq (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution. [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc. October 2019.
3. Donohue K. Prepopik (sodium picosulfate, magnesium oxide, anhydrous citric acid) powder for oral solution. Unified Clinical/Statistical Review. August 9, 2018. Available at: https://www.fda.gov/media/116008/download. Accessed August 9, 2022.
4. Efficacy and Safety of Prepopik in Children for Overall Colon Cleansing in Preparation for Colonoscopy (Prepopik PREA). (2018). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01928862?term=prepopik&draw=2&rank=1. (Identification no. NCT01928862).
5. Prepopik NDA 202535. Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed August 9, 2022.
6. Lee JJ. Clenpiq (sodium picosulfate, magnesium oxide, anhydrous citric acid). Combined CDTL and Signatory Clinical Review. July 31, 2019. Available at: https://www.fda.gov/media/131623/download. Accessed August 9, 2022.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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