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

**Pediatric Postmarketing Pharmacovigilance**

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|---|---|
| **Date:** | May 29, 2019 |
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| **Product Names:** | E-Z-HD, Readi-Cat 2, Readi-Cat 2 Smoothies, Liquid E-Z-Paque, Varibar Pudding (Barium Sulfate) |
| **Pediatric Labeling Approval Date:** | E-Z-HD (January 11, 2016)<br>Readi-Cat 2 and Readi-Cat 2 Smoothies (January 15, 2016)<br>Liquid E-Z-Paque (March 1, 2017)<br>Varibar Pudding (October 14, 2016) |
| **Application Type/Number:** | E-Z-HD (NDA 208036)<br>Readi-Cat 2, Readi-Cat 2 Smoothie (NDA 208143)<br>Liquid E-Z-Paque (NDA 208143-0002)<br>Varibar Pudding (NDA 208844) |
| **Applicant/Sponsor:** | Bracco Diagnostics, Inc |
| **OSE RCM #:** | 2019-570 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for barium sulfate products in pediatric patients less than 17 years of age. 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 serious adverse events associated with barium sulfate in pediatric patients.

Barium sulfate, a radiologic contrast agent, has been marketed as an unapproved drug product for many years for opacification of the gastrointestinal (GI) tract in X-Ray and Computerized Tomography (CT) examinations. FDA approved the first barium sulfate product, E-Z-HD, on January 11, 2016 for use in double-contrast radiographic examinations of the esophagus, stomach, and duodenum to visualize the GI tract in patients 12 years and older. Subsequently, FDA approved additional barium sulfate products for pediatric use in single contrast radiographic examinations of the GI tract, CT of the abdomen, and modified barium swallow examinations.

We reviewed all FAERS reports with barium sulfate products in pediatric patients less than 17 years of age during the period January 11, 2016 to March 7, 2019 and identified one pediatric case with a non-fatal serious outcome. This case described a female patient with a partial obstruction in the distal ileum from congenital bands who developed a complete obstruction with an impacted barium plug following an upper GI series with barium contrast. Patients with severe stenosis at any level of the GI tract are at a high risk for developing obstruction or baroliths, which is well characterized in all barium sulfate labeling.

DPV did not identify any new pediatric safety concerns for barium sulfate products and recommends no regulatory action at this time. We will continue to monitor all adverse events associated with the use of barium sulfate products.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for barium sulfate products in pediatric patients less than 17 years of age. 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 serious adverse events associated with barium sulfate products in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Barium sulfate, a radiologic contrast agent, has been marketed as an unapproved drug product for many years for opacification of the gastrointestinal (GI) tract in X-Ray and Computerized Tomography (CT) examinations. Prior to FDA approval, E-Z-EM, Inc. manufactured and marketed 47 unapproved barium sulfate products produced following US Pharmacopeia (USP) standards.[1] Bracco Diagnostics, Inc acquired EZ-EM, Inc in 2008 and continued to manufacture and distribute unapproved barium products. Bracco Diagnostics proposed to bring barium sulfate products into the new drug approval process and submitted the first New Drug Application (NDA) for E-Z-HD in 2014. This NDA was a literature-based 505(b)(2) submission relying on information from published peer-review papers and review articles, post-marketing data, and professional guidelines issued by the American College of Radiology and European Society of Urogenital Radiology (ESUR).[1] The E-Z-HD NDA was the flagship submission used to cross-reference subsequent barium sulfate NDAs. Table 1 lists current FDA approved barium sulfate products, approval dates, and indications.

**Table 1. Current FDA Approved Barium Sulfate Products**

| NDA/ Supplement | Brand | Approval Date | Route/ Dosage Form | Approved Indications |
|---|---|---|---|---|
| 208036 | E-Z-HD | January 11, 2016 | Oral/ Powder for suspension | Use in double-contrast radiographic examinations of the esophagus, stomach, and duodenum to visualize the gastrointestinal (GI) tract in patients 12 years and older |
| 208036/ S-0002 | E-Z-Cat Dry* | January 3, 2017 | Oral/ Powder for suspension | Use in computed tomography (CT) of the abdomen to delineate the GI tract in adult and pediatric patients |
| 208036/ S-005 | E-Z-Paque | April 7, 2017 | Oral/ Powder for suspension | Use in single contrast radiographic examinations of the esophagus, stomach, duodenum, and small bowl to visualize the GI tract in adult and pediatric patients |
| 208143 | Readi-Cat 2 & Readi-Cat 2 Smoothies | January 15, 2016 | Oral/ Suspension | Use in CT of the abdomen to delineate the GI tract in adult and pediatric patients |
| 208143/ S-0002 | Liquid E-Z-Paque | March 1, 2017 | Oral/ Suspension | Use in single contrast radiographic examinations of the esophagus, stomach, and small bowel to visualize the GI tract in adult and pediatric patients |
| 208143/ S-004 | Varibar Nectar | July 7, 2017 | Oral/ Suspension | Use in modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology in adult and pediatric patients |

| Table 1. Current FDA Approved Barium Sulfate Products | | | | |
|---|---|---|---|---|
| **NDA/ Supplement** | **Brand** | **Approval Date** | **Route/ Dosage Form** | **Approved Indications** |
| 208143/ S-005 | Tagitol V† | August 4, 2017 | Oral/ Suspension | Use in CT colonography as a fecal tagging agent in adults |
| 208143/ S-006 | Varibar Thin Honey | January 23, 2018 | Oral/ Suspension | Use in modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology in adult and pediatric patients |
| 208143/ S-007 | Varibar Honey | March 26, 2018 | Oral/ Suspension | Use in modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology in adult and pediatric patients 6 months of age and older |
| 208844 | Varibar Pudding | October 14, 2016 | Oral/ Paste | Use in modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology in adult and pediatric patients 6 months of age and older |
| * Product has never been manufactured or released to the U.S. market under the approved NDA.<br>† Product is not applicable to this review because it does not have pediatric indications. | | | | |

The pediatric labeling of barium sulfate products was extrapolated from the efficacy and safety data of barium sulfate for delineation of the GI tract in the adult population. This is supported by the published literature, practice guidelines by radiology professional groups, and by Bracco Diagnostics' pediatric use survey data. In lieu of submitting an initial Pediatric Study Plan (iPSP), the Sponsor conducted two surveys, "General Barium Survey" and "Barium Swallow Survey," among product users and medical experts of barium sulfate products in pediatric patients to assess how these products are used. The response rates for both surveys were low at 1.3% (51/3,778 recipients) and 20% (429/2,159 recipients) for "Barium Swallow Survey" and "General Barium Survey," respectively.[1] The "Barium Swallow Survey" targeted Speech Language Pathologies whereas the "General Barium Survey" targeted radiologists or CT/radiology technicians or CT/radiology managers. Each of the two surveys covered all pediatric age groups: birth through 1 month, 1 month to 2 years, 2 to 12 years, and >12 years. The results of the surveys revealed that E-Z-HD and other barium products (e.g., E-Z-Paque, Liquid E-Z-Paque) were used in fluoroscopic exams of the esophagus and upper GI tract across all pediatric age groups.

This review was prompted by the approval of E-Z-HD, Readi-Cat 2, Readi-Cat 2 Smoothie products, Varibar Pudding, and Liquid E-Z-Paque in the pediatric population. DPV has not presented barium sulfate products before the Pediatric Advisory Committee (PAC) in the past.

### 1.2 RELEVANT LABELED SAFETY INFORMATION

Select safety information from the E-Z-Paque (barium sulfate) for oral suspension product label dated April 2017 is included below, though similar language is included in all the other FDA approved barium sulfate products included in Table 1 above: [2]

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

E-Z-PAQUE is contraindicated in patients with the following conditions:

- Known or suspected perforation of the GI tract
- Known obstruction of the GI tract
- High risk of GI perforation such as those with a recent prior GI perforation, acute GI hemorrhage or ischemia, toxic megacolon, severe ileus, post GI surgery or biopsy, acute GI injury or burn, or recent radiotherapy to the pelvis
- High risk of aspiration such as those with prior aspiration, tracheo-esophageal fistula, or obtundation
- With known severe hypersensitivity to barium sulfate or any of the excipients of E-Z-PAQUE

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

**5.1 Hypersensitivity Reactions**

Barium sulfate preparations contain a number of excipients, including natural and artificial flavors and may induce serious hypersensitivity reactions. The manifestations include hypotension, bronchospasm and other respiratory impairments, dermal reactions including rashes, urticaria, and itching. A history of bronchial asthma, atopy, or a previous reaction to a contrast agent may increase the risk for hypersensitivity reactions. Emergency equipment and trained personnel should be immediately available for treatment of a hypersensitivity reaction.

**5.2 Intra-abdominal Barium Leakage**

The use of E-Z-PAQUE is contraindicated in patients at high risk of perforation of the GI tract *[see Contraindications (4)]*.Administration of E-Z-PAQUE may result in leakage of barium from the GI tract in the presence of conditions such as carcinomas, GI fistula, inflammatory bowel disease, gastric or duodenal ulcer, appendicitis, diverticulitis, and in patients with a severe stenosis at any level of the GI tract, especially distal to the stomach. Barium leakage has been associated with peritonitis and granuloma formation.

**5.3 Delayed Gastrointestinal Transit and Obstruction**

Orally administered barium sulfate may accumulate proximal to a constricting lesion of the colon, causing obstruction or impaction with development of baroliths (inspissated barium associated with feces) and may cause abdominal pain, appendicitis, bowel obstruction, or rarely perforation. Patients with the following conditions are at higher risk for developing obstruction or baroliths: severe stenosis at any level of the GI tract, impaired GI motility, electrolyte imbalance, dehydration, on a low residue diet, on medications that delay GI motility, constipation**,** cystic fibrosis, Hirschsprung disease, and the elderly *[see Use in Specific Populations (8.4, 8.5)]*. To reduce the risk of delayed GI transit and obstruction, patients should maintain adequate hydration during and in the days following a barium sulfate procedure. Consider the administration of laxatives.

**5.4 Aspiration Pneumonitis**

The use of E-Z-PAQUE is contraindicated in patients at high risk of aspiration *[see Contraindications (4)]*. Oral administration of barium is associated with aspiration pneumonitis, especially in patients with a history of food aspiration or with compromised swallowing mechanism. Vomiting following oral administration of barium sulfate may lead to aspiration pneumonitis. In patients at risk for aspiration, begin the procedure with a small ingested volume of E-Z-PAQUE. Discontinue administration of E-Z-PAQUE immediately if aspiration is suspected.

**5.5 Systemic Embolization**

Barium sulfate products may occasionally intravasate into the venous drainage of the large bowel and enter the circulation as a "barium embolus" leading to potentially fatal complications which include systemic and pulmonary embolism, disseminated intravascular coagulation, septicemia and prolonged severe hypotension. Although this complication is exceedingly uncommon after oral administration of a barium sulfate suspension, monitor patients for potential intravasation when administering barium sulfate.

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

The following adverse reactions have been identified from spontaneous reporting or clinical studies of barium sulfate administered orally. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure

- Nausea, vomiting, diarrhea and abdominal cramping

- Serious adverse reactions and fatalities include aspiration pneumonitis, barium sulfate impaction, intestinal perforation with consequent peritonitis and granuloma formation, vasovagal and syncopal episodes

**8.4 Pediatric Use**
The efficacy of E-Z-PAQUE in pediatric patients from birth to less than 17 years of age is based on successful opacification of the esophagus, stomach, duodenum and small bowel during radiologic examinations *[see Clinical Pharmacology (12.1)]*. Safety and dosing recommendations in pediatric patients are based on clinical experience *[see Dosage and Administration (2.1)]*.

E-Z-PAQUE is contraindicated in pediatric patients with tracheo-esophageal fistula *[see Contraindications (4)]*. Pediatric patients with a history of asthma or food allergies may be at increased risk for development of hypersensitivity reactions [*see Warnings and Precautions (5.1)]*. Pediatric patients with cystic fibrosis or Hirschsprung disease should be monitored for bowel obstruction after use *[see Warnings and Precautions (5.3)]*. Pediatric patients with hereditary fructose intolerance may develop severe symptoms with administration of E-Z-Paque; assess for this risk and avoid use in patients with hereditary fructose intolerance *[see Warnings and Precautions (5.6)]*.

# 2 METHODS AND MATERIALS

## 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

| **Table 2. FAERS Search Strategy*** | |
|---|---|
| Date of Search | March 12, 2019 |
| Time Period of Search | January 11, 2016† - March 7, 2019 |
| Search Type | Quick Query |
| Product Terms | Product active ingredient: barium sulfate<br>NDA: 208036, 208143, 208844<br>Product name: E-Z-Cat Dry, E-Z-HD, E-Z-Paque, Liquid E-Z-Paque, Readi-Cat 2, Varibar Honey, Varibar Nectar, Varibar Pudding, Varibar Thin Honey |
| MedDRA Search Terms (Version 21.1) | All Preferred Terms (PT) |
| * See Appendix A for a description of the FAERS database.<br>† Approval date of E-Z-HD (NDA 208036), first approval barium sulfate product in this review. | |

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

Table 3 presents the number of adult and pediatric FAERS reports from January 11, 2016 to March 7, 2019 with barium sulfate.

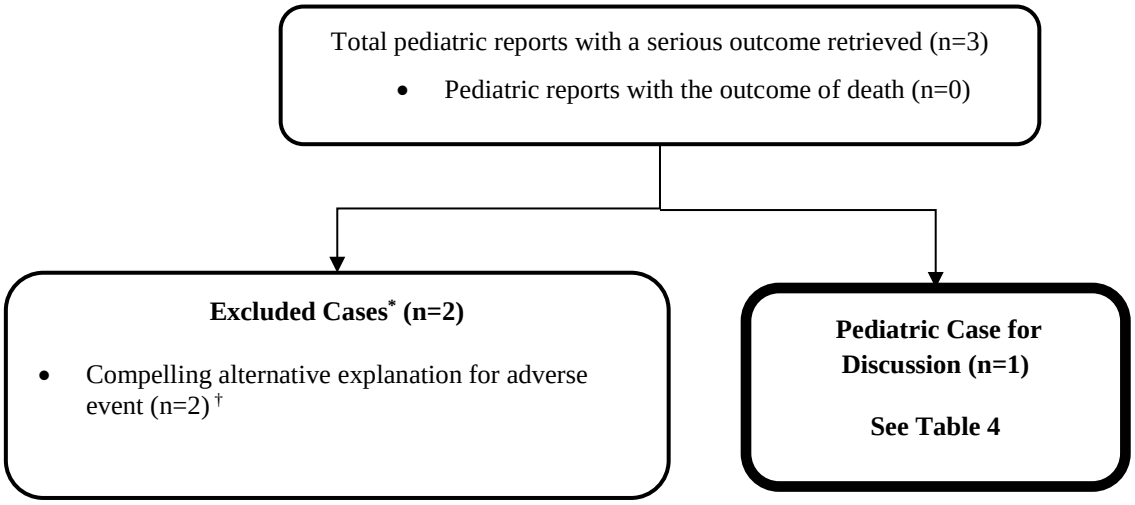
| Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from January 11, 2016 to March 7, 2019 with Barium Sulfate | | | |
|---|---|---|---|
| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 17 years) | 129 (113) | 38 (22) | 3 (0) |
| Pediatrics (0 - <17 years) | 9 (7) | 3 (1) | 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, and other serious important medical events.

### *3.1.2 Selection of Serious Pediatric Cases in FAERS*

Our FAERS search retrieved three serious pediatric reports from January 11, 2016 to March 7, 2019. Although we reviewed the three pediatric reports in FAERS with a serious outcome, we excluded two reports from the case series for further discussion because the report contained compelling alternative explanations for the adverse event. We summarize the remaining case in the sections below.

**Figure 1. Selection of Serious Pediatric Cases with Barium Sulfate**




* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed below.

† Both cases are derived from the medical literature. One case described bacteremia with fecal flora secondary to gut bacteria translocation after intussusception reduction with barium enema.[3] The second case described transient respiratory distress without resultant pneumonitis following accidental barium injection into the right bronchus during evaluation for tracheoesophageal fistula.[4]

### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

We did not identify any fatal pediatric adverse event cases.

### *3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=1)*

We identified one serious FAERS case with barium sulfate in the pediatric population reporting a non-fatal serious outcome. The narrative summary is described below.

FAERS Case #15881943, USA, Expedited, FDA Received Date January 1, 2019
A literature case[5] reported a female newborn (weight 2,560 grams) with a partial bowel obstruction on the first day of life. On day 2 of life, she had an upper gastrointestinal (GI) series with barium contrast to evaluate the etiology of her intestinal obstruction. The patient subsequently developed a complete bowel obstruction and underwent an exploratory laparotomy on day 4 of life, which showed a partial intestinal obstruction in the distal ileum from a congenital band that was rendered complete by an impacted barium plug. The congenital band was subsequently lysed and a proximal enterotomy was performed to evacuate the three by one centimeter intraluminal coagulated barium plug. The patient was discharged on day 23 of life without complications.

*Reviewer's comments: All barium sulfate products are labeled for GI obstruction in the Warnings and Precautions section of the product label.[2] Patients with severe stenosis at any level of the GI tract are at a high risk for developing obstruction or baroliths. The high viscosity of the barium delays transit through the bowel, allowing continued absorption of water from the barium preparation and causing precipitation resulting in formation of barolith.[5]*

## 4 DISCUSSION

We reviewed all serious FAERS reports with barium sulfate in the pediatric population (ages 0 - < 17 years) during the period January 11, 2016 to March 7, 2019 and identified one case for discussion. The single report described a labeled event of GI obstruction in a patient who was at increased risk for this adverse event due to partial obstruction from congenital bands. We did not identify any new safety signals, or an increased severity or frequency of any labeled adverse events, or any fatalities directly associated with barium sulfate.

## 5 CONCLUSION

The adverse event described in the FAERS case is consistent with the known safety profile described in the current barium sulfate label. DPV did not identify any pediatric safety concerns for barium sulfate at this time.

## 6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of barium sulfate.

## 7 REFERENCES


1. Ye B. New Drug Application, Barium Sulfate Powder for Suspension (NDA 208036) Clinical Review. November 16, 2015. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM489008.pdf. Accessed March 15, 2019.
2. Bleich K. Division of Medical Imaging Products (DMIP) Clinical Review (NDA 020351 Supplement 44). Visipaque (Iodixanol) Injection. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM576295.pdf March 10, 2017. Accessed March 28, 2019.
3. Chang H, Hu HH, Cheng MF, et al. Septicemia after Barium Reduction in a Pediatric Patient with Intussusception. *Pediatr Neonatol.* 2017;58(1):93-94.
4. De Bernardo G, Sordino D, Giordano M, Doglioni N, Trevisanuto D. Persistent bronchography in a newborn with esophageal atresia. *Radiol Case Rep.* 2016;11(2):113-115.
5. Den J, Bowen-Jallow K, Tran S. Barium impaction causing bowel obstruction in a neonate. *Journal of Pediatric Surgery Case Reports.* 2019;41:37-39.

# 8 APPENDICES

## 8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

**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.

## 8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

| | Initial FDA Received Date | FAERS Case # | Version # | Manufacturer Control # | Case Type | Age (days) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1/28/2019 | 15881943 | 1 | US-BRACCO-2018US06557 | Expedited | 1 | Female | USA | OT |

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviation: OT=Other medically significant

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