NDA Clinical Review and Evaluation

Application Type	Type 3, 505(b)(2)
Application Number(s)	NDA 219840
Priority or Standard	Standard
Submit Date(s)	November 21, 2024
Received Date(s)	November 21, 2024
PDUFA Goal Date	September 21, 2025
Division/Office	Division of Imaging and Radiation Medicine/Office of Specialty Medicine
Review Completion Date	July 30, 2025
Established/Proper Name	Barium sulfate
Trade Name	E-Z-Disk
Pharmacologic Class	Radiographic contrast agent
Applicant	Bracco Diagnostics Inc.
Dosage Form	Tablet
Applicant Proposed Dosing Regimen	The recommended oral dose of E-Z-DISK is one tablet
Applicant Proposed Indication	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term	(b) (4) (disorder)
Regulatory Action	Approval
Recommended Indication	For the evaluation of esophageal patency in adults and pediatric patients aged 12 years and older
Recommended SNOMED CT Indication Disease Term	405247003 | Obstruction of esophagus (disorder)
Recommended Dosing Regimen	The recommended dose of E-Z-DISK in adults and pediatric patients aged 12 years and older is one 700 mg tablet orally during imaging.

1 Therapeutic Context

1.1. Analysis of Condition

One of the most common indications for evaluation of the upper digestive tract is difficulty in swallowing (dysphagia). Dysphagia is not specific for a particular pathology, but instead can result from numerous abnormalities including functional (i.e., achalasia, esophageal dysmotility) and anatomic (i.e., stricture, esophagitis) esophageal and non-esophageal conditions. Patients with dysphagia are often imaged using fluoroscopic esophagram.

Esophagrams require the administration of contrast as the esophagus is otherwise essentially not visualized by fluoroscopy. Barium sulfate suspension is typically used due to its favorable x-ray absorption characteristics, availability, and long-standing history of clinical use. However, it can be valuable to employ solid materials during an esophagram. Transit of solids may arrest at a site of pathology in some cases. Further, in patients who present with dysphagia of solids but not liquids, correlating symptoms occurring during swallowing of a solid bolus directly with imaging may reveal an abnormality not seen with liquid contrast or may futher characterize the relevance of an abnormality seen using liquid contrast. E-Z-Disk is a barium sulfate tablet intended to provide a radiopaque solid bolus of reproducible size and shape.

There are variable reports of the diameter at which dysphagia will begin to occur in patients who have esophageal stricture or ring, but 13 mm is a commonly cited threshold. The 11.5 mm to 13.5 mm (approximately 1/2 inch) diameter of E-Z-Disk is near this threshold, and lack of arrest of the tablet in the esophagus has been proposed to indicate that causes of dysphagia other than esophageal stricture should be considered.

1.2. Analysis of Current Treatment Options

Some iodinated contrast agents are indicated for evaluation of the upper gastrointestinal tract, and are preferred over barium sulfate for certain indications such as suspected perforation or leak. However, they are not available in solid dosage forms.

Foods such as marshmallow can be used as a solid bolus, either swallowed with thin barium sulfate suspension (negative contrast) or coated with barium sulfate powder. Food boluses are generally not standardized in size or shape.

Endoscopy can be used to diagnose and, in some conditions such as stricture, treat esophageal disorders causing dysphagia. Its invasive nature is the major drawback.

2 Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

E-Z-Disk is a marketed, unapproved product.

2.2. Summary of Presubmission/Submission Regulatory Activity

As noted in the summary of regulatory history in the Division Director Summary Review for NDA 208036 dated January 4, 2016:

> *The FDA and the Applicant agreed that the E-Z-HD NDA would contain all the clinical study data in support of* [redacted] (b) (4) *barium sulfate products in the US. As such a full review of all the applicable clinical studies was conducted at the time of the first NDA submission.*

Type C guidance meeting comments (converted to written responses only) were communicated on November 14, 2023. Comments related to E-Z-Disk included a recommendation to conduct a nonclinical safety evaluation for any excipients and impurities new to E-Z-Disk and the statement that [redacted] (b) (4) would be best supported by reference standard-based performance data.

Refer to the NDA 208036 review for a summary of regulatory interactions regarding barium sulfate products, including E-Z-Disk, that occurred prior to E-Z-HD approval.

3 Review Strategy

Clinical data for this NDA are included by cross-reference to NDA 208036. NDA 208036 includes several barium sulfate powder for suspension products, with E-Z-HD being the first approved. The Applicant and FDA agreed that this 'flagship' NDA could contain the clinical and nonclinical data for other barium sulfate formulations. Clinical data in the flagship NDA were reviewed for all products with intent to rely on the clinical review for NDA 208036 dated November 17, 2015, during subsequent NDAs. That review is incorporated here by reference.

As for prior barium sulfate NDAs, evidence of diagnostic use of barium sulfate tablets is considered supportive. The Applicant has cited a published study that examined the ability of a barium sulfate tablet to identify patients with unsuspected esophageal pathology (Ghahremani et al. 1996). This study will be reviewed in the next section.

4 Clinical Evaluation

4.1. Review of Relevant Individual Trials Used to Support Efficacy

4.1.1. (Ghahremani et al. 1996)

This was a prospective, single-arm cohort study conducted at a single center in the United States. It enrolled adults older than 40 years who were referred for chest radiography for an indication unrelated to the upper gastrointestinal tract. Patients with solid dysphagia, history of aspiration, or history of treatment for esophageal disorders were excluded.

Prior to obtaining the chest radiograph, patients were asked to swallow one barium sulfate tablet with 100 mL water. The tablet used for this study was Bar-Test (650 mg barium sulfate) rather than E-Z-Disk (700 mg barium sulfate). The composition of these tablets is very similar (Table 1). After tablet administration, standard posteroanterior and lateral views of the chest were obtained and promptly reviewed for retention of the tablet in the esophagus. Identity of the reviewers and methods of review were not stated. Patients who were identified as having tablet retention in the esophagus were asked to proceed to double contrast esophagram. The esophagram was interpreted as a standard clinical procedure and details of the readers or interpretation criteria were not reported.

Table 1. Comparison of Bar-Test and E-Z-Disk Composition

Component Name	Function	Bar-Test Percent Composition (% w/w)	E-Z-Disk Percent Composition (% w/w)
Barium sulfate (1 micron)	Contrast agent	(b) (4)	(b) (4)
Description		Flat side tablet 12.5 mm diameter	Flat-sided tablet 11.5 - 13.5 mm diameter
Confectioner's sugar	(b) (4)	(b) (4)	(b) (4)
Corn starch			
Povidone			
Microcrystalline cellulose			
Croscarmellose sodium			
Magnesium stearate			

Source: Response to Information Request, April 9, 2025, Table A

A total of 300 patients were enrolled, including 162 males (54%). The mean age was 65 years, with a range of 43 years to 87 years. Race and ethnicity information was not reported.

All 300 patients received the barium sulfate tablet and chest radiographs. The tablet was found in the esophagus on at least one view in 20 patients (7%), and these patients proceeded to have

an esophagram. Three of these patients had the tablet in the esophagus only on the first chest radiograph view, suggesting delayed transit without fixed high grade obstruction. These patients had tertiary contractions or segmental spasm on esophagram without anatomic abnormality. The remaining 17 patients (6%) demonstrated retention of the tablet in the esophagus on the second (final) view. Their findings on esophagram are listed in Table 2. Two patients had normal esophagrams. The most common type of abnormality was stricture or ring, observed in ten patients. If test positivity is defined as tablet retention in the esophagus on both chest radiograph views and reference standard positivity as any abnormality on esophagram, the positive predictive value of the test would be 15/17 (88%, 95% confidence interval: 64%, 99%). The prevalence of esophageal disorders in patients without symptoms referrable to the esophagus, essentially a screening population, is expected to be relatively low, though this was not verified in the study as reference standard data were not collected in most patients.

Table 2. Findings on Esophagram Among Patients with Retained Barium Sulfate Tablet in the Esophagus

Case no.	Sex	Age (yr)	Level of retention	Underlying etiology
1	F	76	Proximal esophagus	Zenker diverticulum and prominent cricopharyngeus muscle
2	F	53	Proximal esophagus	Segmental esophagitis associated with heterotopic gastric mucosa
3	M	46	Proximal esophagus	Normal (false positive)
4	M	69	Middle esophagus	Benign stricture after right upper lobectomy for granuloma
5	F	73	Middle esophagus	Benign stricture following coronary artery bypass surgery
6	F	74	Middle esophagus	Malignant stricture by metastasis after bilateral mastectomy
7	F	72	Middle esophagus	Extrinsic compression by the left main stem bronchus
8	F	78	Middle esophagus	Diffuse esophageal spasm
9	F	74	Middle esophagus	Normal (false posistive)
10	F	76	Distal esophagus	Schatzki ring and hiatus hernia
11	M	63	Distal esophagus	Schatzki ring and hiatus hernia
12	F	60	Distal esophagus	Schatzki ring and hiatus hernia
13	F	84	Distal esophagus	Peptic stricture, reflux esophagitis
14	M	65	Distal esophagus	Peptic stricture, reflux esophagitis
15	M	58	Distal esophagus	Peptic stricture, reflux esophagitis
16	M	66	Distal esophagus	Peptic stricture, reflux esophagitis
17	F	79	Distal esophagus	Esophageal dysmotility and extrinsic compression due to cardiomegaly

Source: (Ghahremani et al. 1996), Table 1

This study supports diagnostic utility of E-Z-Disk in disorders of the esophagus through documenting visualizability of barium sulfate tablets and association of esophageal tablet retention with anatomic and functional abnormalities. There were differences in mass of barium sulfate, tablet formulation, and imaging technique in this study as compared to the anticipated clinical use of E-Z-Disk. However, for the limited conclusions drawn from the study in this review, these differences do not affect the applicability of the results to E-Z-Disk.

4.1.2. Integrated Assessment of Effectiveness

The Applicant indicated that they have not conducted clinical trials and are relying on literature, guidelines, and post-marketing experience involving barium sulfate products. These were reviewed in flagship NDA 208036 and found to provide evidence of effectiveness for barium sulfate products including E-Z-Disk. During this review cycle, the scientific literature was

searched for additional relevant publications since 2015. None of the new publications raised concern regarding effectiveness of E-Z-Disk.

(Ghahremani et al. 1996) is not, and is not intended to be, an adequate and well-controlled trial, and it does not provide substantial evidence of effectiveness for E-Z-Disk. However, it does support clinical utility of barium sulfate tablets such as E-Z-Disk for visualizing esophageal anatomy and pathology.

(b) (4)

conditions such as extrinsic compression and dysmotility could lead to failure of the tablet to reach the stomach. (b) (4) the evidence of diagnostic use established in the review of NDA 208036 and in (Ghahremani et al. 1996) are adequate to support a structure delineation indication. Specifically for E-Z-Disk, visualization of the tablet traversing the esophagus is consistent with patency to solids the size of the tablet or smaller.

4.2. Review of Safety

4.2.1. Safety Review Approach

E-Z-Disk contains 700 mg barium sulfate, an amount much less than the recommended dose for several approved oral barium sulfate products. For example, the recommended dose for E-Z-Paque is equivalent to 169 g to 450 g barium sulfate and for E-Z-HD is equivalent to 155 g to 321 g. In addition, it is anticipated that E-Z-Disk will most often be used in conjunction with a barium sulfate suspension product as part of an esophagram or upper gastrointestinal series imaging study. Therefore, it is reasonable to rely on other oral barium products for much of the safety profile. Reference is made to the flagship NDA 208036 clinical review.

The formulation of E-Z-Disk as a tablet raises a safety issue that is not present with currently approved barium sulfate formulations, tablet retention. This is reviewed in the next section.

4.2.2. Analysis of Submission-Specific Safety Issues

Tablet retention

The risk of retention in the esophagus is present for any solid dosage form and increases with size, among other factors. However, this risk is particularly important to consider for E-Z-Disk because it is relatively large, typically administered to symptomatic patients with known or suspected esophageal narrowing, and intended to lodge at sites of stenosis of sufficient severity to cause dysphagia. Prolonged lodgement could lead to esophageal obstruction or esophagitis. Accordingly, E-Z-Disk is intended to disintegrate promptly in the gastrointestinal tract.

A published case series reported two patients at a single institution that experienced

esophageal obstruction following administration of barium sulfate tablets (Schabel and Skucas 1977). The tablets were 650 mg barium sulfate tablets manufactured by Vitarine Co., Inc. rather than E-Z-Disk, but of similar size (12.5 mm) and inactive ingredients (sugar, corn starch, sorbital, microcrystalline cellulose, and magnesium stearate). A barium sulfate tablet lodged at a site of distal esophageal narrowing in each patient and produced symptomatic obstruction lasting 3 hours in one patient and more than 6 hours in the other patient. The authors noted that the tablets came from a single package that had been obtained at least 3 years prior and hypothesized that older tablets may disintegrate more slowly than fresh tablets.

A search of the FDA Adverse Event Reporting System (FAERS) database revealed one report of a patient who experienced retention of an E-Z-Disk tablet in the esophagus during an esophagram performed for difficulty swallowing. The report did not comment on degree of obstruction or symptoms associated with the retention. After 2.5 hours, during which water was administered, the tablet disintegrated. A sample from the same lot was tested and met specifications. The manufacturer noted that storage conditions of the tablets at the clinical site were unknown and that storage conditions might affect disintegration rate.

In vitro tablet disintegration testing is performed (b) (4). While the in vitro conditions are likely quite different from those in the esophagus, this testing remains an important risk reduction strategy. Additionally, the prescribing information contains the statement, "E-Z-DISK is formulated to disintegrate within the gastrointestinal (GI) tract. In the event of prolonged retention, consider implementing appropriate interventions," to promote awareness of the issue. Importantly, retention of the tablet in the esophagus will be evident on imaging performed according to E-Z-Disk's intended use.

4.2.3. Integrated Assessment of Safety

Because of the long standing use of barium sulfate products, safety of the drug is relatively well understood. Warnings from previously approved barium sulfate suspension/for suspension formulations, including hypersensitivity reactions, barium leakage, delayed gastrointestinal transit and obstruction, aspiration pneumonitis, and systemic embolization as well as related contraindications will be retained. The adverse reaction profile is expected to be essentially identical to previously approved barium sulfate products.

4.3. Conclusions and Recommendations

The clinical reviewer concurs with the reviewers of flagship NDA 208036 that the totality of the evidence for E-Z-Disk supports its utility for a structure delineation indication of the esophagus. Long standing use of barium sulfate tablets, including E-Z-Disk, has shown a favorable safety profile. The benefit-risk balance of E-Z-Disk is favorable and approval of this application is recommended.

5 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held, and no external consultations were requested for this NDA.

6 Pediatrics

(b) (4)

E-Z-Disk can be used to visualize the esophagus, including in patients with suspected stricture, and passage of the tablet is consistent with esophageal patency to solids of ~13 mm and smaller. Conditions that narrow the esophageal lumen in pediatric patients, such as stricture after caustic ingestion or at a surgical anastomosis, are often readily evaluated using liquid contrast agents. In addition, they typically occur in very young patients who have not yet learned to ingest solid materials safely.

However, there are some pediatric patients who might benefit from availability of E-Z-Disk. It is reasonable to base effectiveness on studies of other barium sulfate products reviewed in flagship NDA 208036, in the same manner as effectiveness of E-Z-Disk is being supported in adults. Of important note, since the tablet must be swallowed intact, any indicated pediatric age group must have an appropriate native esophageal diameter. Based largely on a report of normal esophageal diameter at esophagram by age (Life et al. 2024), the Applicant proposed indicating E-Z-Disk for pediatric patients 12 years old and older. This referenced study measured anteroposterior and lateral diameters of the proximal, mid, and distal esophagus. The proximal esophagus had the narrowest caliber. The lower bound of the 95% confidence interval of the wider (anteroposterior) diameter of the proximal esophagus was 13 mm or smaller in patients <11 years old and 14 mm or larger in patients 11 years and older. While published tablet swallowability data suggest a 13.5 mm tablet can be administered to younger children, the related rate of tablet arrest in normal patients might increase.

As such, indicating E-Z-Disk in pediatric patients 12 years old and older appears reasonable. The small number of pediatric patients below the age of 12 in whom a barium sulfate tablet would be expected to provide meaningful benefit over liquid contrast supports a waiver of pediatric assessment in this younger population.

The safety of barium sulfate has previously been established in children. Relevant contraindications and warnings such as those for tracheoesophageal fistula and aspiration are retained in the prescribing information.

7 Risk Evaluation and Mitigation Strategies (REMS)

A risk evaluation and mitigation strategy was not needed for this NDA.

8 Postmarketing Requirements and Commitment

No clinical postmarketing requirement or commitment is needed for this application.

9 Appendices

9.1. References

Ghahremani, G. G., J. P. Weingardt, K. R. Curtin and V. Yaghmai (1996). "Detection of occult esophageal narrowing with a barium tablet during chest radiography." Clin Imaging 20(3): 184-190.

Life, C. S., B. D. Buck, C. Gardner, L. Silveira, M. Boehnke, S. S. Milla and K. Hayes (2024). "Establishing normal values for pediatric esophageal diameter on fluoroscopy." Pediatr Radiol 54(13): 2220-2226.

Schabel, S. I. and J. Skucas (1977). "Esophageal obstruction following administration of "aged" barium sulfate tablets--a warning." Radiology 122(3): 835-836.

9.2. Financial Disclosure

No covered clinical studies were included in this application.

9.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	The patient experience data that were submitted as part of the application include:			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		

	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify):	
□	Patient experience data that were not submitted in the application, but were considered in this review:		
	□	Input informed from participation in meetings with patient stakeholders	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	Patient experience data were not submitted as part of this application and were not needed.		

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