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APPLICATION NUMBER:

219840Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	219840
Supporting document/s:	001
Applicant's letter date:	November 21, 2024
CDER stamp date:	November 21, 2024
Product:	E-Z-Disk (Barium Sulfate) Tablets
Indication:	(b) (4)
Applicant:	BRACCO DIAGNOSTICS, INC.
Review Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM) in support of the Division of Imaging and Radiation Medicine
Reviewer:	Ronald Honchel, Ph.D.
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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Barium sulfate has been used since the early 1900's as a positive contrast agent for radiographic studies. Barium sulfate has a high molecular density relative to soft tissues allowing for increased X-ray absorption and delineation of the gastrointestinal (GI) tract. The Sponsor stated that the safety and efficacy of barium sulfate imaging products have been well established with more than a 100 years of clinical use experience. The Sponsor and the Division of Imaging and Radiation Medicine (Division of Medical Imaging Products or DMIP) previously agreed to submitting 505(b)(2) NDA applications based on the publically available data for the barium sulfate containing products marketed by the Sponsor. This application is the 4th of the barium sulfate applications submitted by the Sponsor with the first 3 NDA applications (NDA 208036, NDA 208143, and NDA 208844) already approved.

1.2 Brief Discussion of Nonclinical Findings

As previously agreed, the Sponsor cross-referenced NDA 208036, the first of the barium sulfate NDAs submitted to the FDA. As pointed out in the NDA 208036 nonclinical review, the LD_{50} of intragastrically administered barium sulfate (150% w/v) was calculated to be 364 g/kg in young (130-160 g) male CBL-Wistar albino rats. The cause of death was stomach rupture. No other relevant nonclinical studies or findings for barium sulfate were reported in the literature. Like NDA 208036, nonclinical cannot recommend approval of this NDA application from a discipline perspective due to the lack of nonclinical data. Nonetheless, there is extensive clinical experience with barium sulfate. If clinical determines that there is adequate clinical safety data to support approval; nonclinical will concur.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, NDA approval should be based on the adequacy of the available clinical safety data for which nonclinical defers to clinical.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

There were no nonclinical recommended edits for the proposed labeling with the exception of changing the established pharmacologic class from (b) (4) contrast agent to radiographic contrast agent.

2 Drug Information

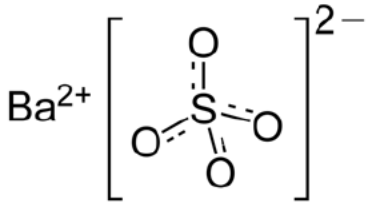
2.1 Drug

Code Name: E-Z-Disk Tablets

Chemical Name: Barium sulfate

Molecular Formula/Molecular Weight: $BaSO_4$/233.39 g/mol

Structure:



Pharmacologic Class: Radiographic Contrast Agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

The Sponsor cross-referenced NDA 208036, the first barium sulfate NDA that the Sponsor submitted to the Division.

2.3 Drug Formulation

Table A: E-Z-DISK Drug Product Composition

Confab Component Number	Component Name	Percent composition (% w/w)	Amount (mg) per tablet	Function	Grade
(b) (4)	Barium sulfate (b) (4)	(b) (4)			Pharmaceutical
	Confectioner's Sugar				USP/NF
	Corn Starch				USP/NF
	Povidone				USP
	Microcrystalline Cellulose				USP/NF
	Croscarmellose Sodium				USP/NF
	Magnesium Stearate				USP/NF

[a] The (b) (4) Barium Sulfate is the EZEM code (b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients used in E-Z-Disk tablets.

2.5 Comments on Impurities/Degradants of Concern

The barium sulfate drug substance contains a number of impurities. In NDA 208036, the Sponsor proposed impurity limits and provided an expert opinion toxicology report to support the safety of those proposed limits. From the Nonclinical Reviewer's perspective, the only firm conclusion one could make for some of the evaluations provided in the expert opinion toxicology report was that the proposed impurity limit was "probably safe" as the data for some of the impurities was limited and the methods used for determining safety were inconsistent. Nonetheless, the impurity limits proposed by the Sponsor seem reasonable given that barium sulfate has been around so long. For example, the impurity limit set for (b) (4) in the drug substance was set at NMT (b) (4)% w/w. The (b) (4) levels in 13 recent batches of drug substance ranged from (b) (4)%. While the information provided in the expert opinion document supported that a (b) (4)% w/w impurity limit for (b) (4) is probably safe, that (b) (4)% and greater (b) (4) is apparently common in the drug substance strongly supports the safety of the NMT (b) (4)% limit.

2.6 Proposed Clinical Population and Dosing Regimen

Adults swallow one tablet with one or two swallows of water. Please refer to the clinical review for the proposed clinical population.

2.7 Regulatory Background

The Sponsor and DMIP agreed to submitting 505(b)(2) NDA applications based on the publically available data for a number of the barium sulfate containing drug products marketed by the Sponsor.

3 Studies Submitted

None.

4 Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

N/A

6 General Toxicology

N/A

7 Genetic Toxicology

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

Although barium sulfate has been used clinically since the early 1900's as a positive contrast agent for radiographic studies, there was only one manuscript available that was relevant for evaluating the approvability of barium sulfate from a nonclinical perspective. As reported by Boyd et al. (*Canad. Med. Ass.* J. **94:** 849-853, 1966), the LD_{50} of intragastrically administered barium sulfate was calculated to be 364 g/kg in young male rats. The cause of death was stomach rupture. The Sponsor did submit an Environmental Protection Agency (EPA) report titled "Toxicological Reviews of Barium and Compounds"; however, the EPA report primarily dealt with environmental barium exposure that was not generally relevant to evaluating the safety of barium sulfate when used as a contrast agent.

Barium sulfate is biologically inert (thus not metabolized) and systemic barium sulfate is eliminated unchanged mainly in the feces and urine. Although generally poorly absorbed, statistically significant increases in blood and urine barium levels have been reported in humans after ingesting 58 to 400 g barium sulfate in radiopaque contrast materials (Claval et al., *Therapie* **42:** 239-243,1987). The Sponsor routinely states that barium sulfate absorption is negligible; however, the Sponsor did not provide adequate data to support this statement. Nonetheless, there is strong evidence that barium absorption is relatively low following high dose oral administration of barium sulfate with no additional absorption observed with increasing barium sulfate dose once the ability of gastric acid to liberate barium ions has been exceeded. Additionally, there are no nonclinical concerns with the inactive ingredients present in E-Z-Disk.

Like the Sponsor's previous barium sulfate NDAs, nonclinical cannot make a recommendation that this NDA application should be approved based on the nonclinical data due to the lack of nonclinical data. As described in the previous paragraph and based on the review of the McCauley & Washington manuscript (*Drug Chem Toxicol* **6:**209-217, 1983), there is likely some systemic exposure to barium following the oral administration of barium sulfate. Published reports/studies on the ingestion of more soluble barium salts clearly indicate that toxicity will be observed if enough barium is absorbed. Neither barium absorption at clinically relevant barium sulfate doses nor the blood/tissue barium levels that produce toxicity have been adequately evaluated. Nonetheless, there is extensive clinical experience with barium sulfate. From a

nonclinical perspective, the drug product is approvable from a safety standpoint if clinical determines that there is adequate clinical safety data to support approval.

12 Appendix/Attachments

None.

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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07/16/2025 11:21:19 AM

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