CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208844Orig1s000

PHARMACOLOGY 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:	208844
Supporting document/s:	001
Applicant's letter date:	December 14, 2015
CDER stamp date:	December 14, 2015
Product:	VARIBAR PUDDING, (b)(4)% barium sulfate paste (w/v)
Indication:	For Use in Adult and Pediatric Patients for Modified Barium Swallow Examinations to Evaluate the Oral and Pharyngeal Function and Morphology
Applicant:	BRACCO DIAGNOSTICS, INC.
Review Division:	Medical Imaging
Reviewer:	Ronald Honchel, Ph.D.
Supervisor/Team Leader:	Adebayo Laniyonu, Ph.D.
Division Director:	Libero Marzella, M.D., Ph.D.
Project Manager:	Frank Lutterodt

Template Version: September 1, 2010

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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 DMIP 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 3rd of the barium sulfate applications submitted by the Sponsor with the first 2 NDA applications (NDA 208036 and NDA 208143) 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 Non Clinical Recommendations

None.

1.3.3 Labeling

Proposed by the Sponsor:

8.1 Pregnancy

Risk Summary

(b) (4)

[see Clinical Pharmacology (12)]

8.2 Lactation

Risk Summary

(b) (4)

[see Clinical Pharmacology (12)]

Recommended based on labeling approved for NDA 208036

8.1 Pregnancy

Risk Summary

VARIBAR PUDDING is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug.

8.2 Lactation

Risk Summary

VARIBAR PUDDING is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the infant to the drug.

Proposed by the Sponsor:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the carcinogenic potential of barium sulfate or potential effects on fertility. (b) (4)

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Recommended based on labeling approved for NDA 208036

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the carcinogenic potential of barium sulfate or potential effects on fertility.

2 Drug Information

2.1 Drug

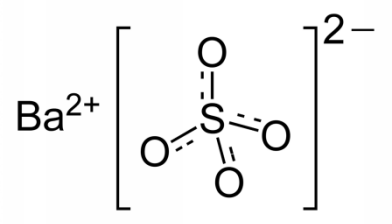
CAS Registry Number: 7727-43-7

Code Name: VARIBAR PUDDING, (b) (4)% barium sulfate paste (w/v)

Chemical Name: Barium sulfate

Molecular Formula/Molecular Weight: $BaSO_4$/233.39

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 they submitted to the Division.

2.3 Drug Formulation

VARIBAR PUDDING consists of 230 mL barium sulfate paste ((b) (4) % w/v) in a (b) (4) multi-use white polyethylene tube. The composition is shown in the Sponsor's Table below.

Table A: Drug Product Composition

Component number	Component Name	Percent composition (% w/v)	Amount (g) per unit (230 mL)	Function	Grade
(b) (4)	Barium sulfate (b) (4)	40.0000[b]	92.000	Contrast agent	USP
	Sodium Benzoate			(b) (4)	USP/NF
	Potassium Sorbate				USP/NF
	Xylitol				USP/NF
	Citric Acid (b) (4)				USP
	Simethicone Emulsion (b) (4)				USP
	Polysorbate 80				USP/NF
	Glycerin				USP
	Xanthan Gum				USP/NF
	Carboxymethylcellulose Sodium				USP
	Maltodextrin				USP/NF
	Ethyl Vanillin				USP/NF
	Artificial Vanilla Flavor[a]				GRAS; 21CFR 172.5 compliant
	Saccharin Sodium				USP

Component number	Component Name	Percent composition (% w/v)	Amount (g) per unit (230 mL)	Function	Grade
(b) (4)	Purified Water			(b) (4)	USP
					(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients used in VARIBAR PUDDING.

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 were "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

As stated in the draft labeling, VARIBAR PUDDING is indicated for use in adult and pediatric patients for modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology. (b) (4)

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 products marketed by the Sponsor. This NDA for VARIBAR PUDDING is the third of those products to be submitted to the FDA.

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 and 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 has 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 VARIBAR PUDDING.

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.

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/s/

RONALD HONCHEL
07/22/2016

ADEBAYO A LANIYONU
07/22/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208-844 **Applicant:** Bracco Diagnostics Inc. **Stamp Date:** December 14, 2015

Drug Name: Barium Sulfate Paste, (b)(4)% - Varibar Pudding **NDA/BLA Type:** 505(b)2

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A. The Sponsor is cross-referencing approved NDA 208036 for all pharmacology/toxicology information as per previous agreement between the Sponsor and the Division.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A. See above.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A. See above.
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A. See above.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A. The labeling to be recommended for this application will be determined in future labeling meetings.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)		X	Nonclinical will be relying on CMC to identify any potential impurity issues.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			N/A.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

RONALD HONCHEL
02/08/2016

ADEBAYO A LANIYONU
02/12/2016