CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213135Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	June 6, 2019
From:	Division of Pediatric and Maternal Health (DPMH) Kerri-Ann Jennings, MS, BSN, RN Senior Regulatory Project Manager
To:	Division of Gastroenterology (DG)
NDA Number:	NDA 213135
Drug:	SUTAB (sodium sulfate, magnesium sulfate, potassium chloride)
Applicant:	Braintree Laboratories, Inc.
Indication:	Bowel preparation prior to colonoscopy in adults

The Division of Gastroenterology (DG) formerly, the Division of Gastroenterology and Inborn Errors Products (DGIEP), submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) on June 6, 2019 requesting evaluation of the relevant PLLR labeling for appropriate statements, for the above referenced NDA.

DPMH completed an initial consult review of NDA 213135 on November 15, 2019. During the initial review cycle, DGIEP decided that the application would receive a Complete Response (CR) action. The Applicant resubmitted the application on May 12, 2020. This is the second review cycle for NDA 213135. However, DPMH was not formally consulted, but participated in applicable internal team meetings from June 8, 2020 through September 25, 2020 to discuss the application. DPMH did not contribute to the labeling during the current review cycle as labeling recommendations did not change from the prior review.

DPMH- Maternal Health has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Kristie Baisden, D.O., F.A.C.O.G.
DPMH Maternal Health Team Leader- Tamara Johnson, MD, MS
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Kerri-Ann Jennings, MS, BSN, RN

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/s/

KERRI-ANN JENNINGS
10/16/2020 10:48:06 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 29, 2020

To: Anum Shami, Regulatory Project Manager (DG)

Joette Meyer, Associate Director for Labeling (DG)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader (OPDP)

Subject: OPDP Labeling Comments for SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, for oral use

NDA: 213135

In response to DG's consult request dated June 5, 2020, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for Sutab.

Labeling: OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail from DG on September 25, 2020. Additionally, the email indicated that only the PI has been edited since the last review, so that is the only item to review at this time.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 8, 2020
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213135
Product Name, Dosage Form, and Strength:	Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, 1.479 g, 0.225 g, and 0.188 g per tablet
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Braintree
FDA Received Date:	March 11, 2020 and May 12, 2020
OSE RCM #:	2019-1052-3
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

Braintree submitted a response to the complete response (CR) for NDA 213135 on Mary 12, 2020. As part of the approval process for Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, the Division of Gastroenterology (DG) requested that we review the proposed Sutab prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 213135 received a CR on March 13, 2020 due to manufacturing facility deficiencies.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Braintree submitted a 505(b)(2) NDA for Sutab (sodium sulfate, magnesium sulfate, and potassium chloride). We reviewed the prescribing information, carton labeling, and container label. The proposed PI, carton labeling, and container label are acceptable.

5 CONCLUSION & RECOMMENDATIONS

The proposed PI, carton labeling, and container label are acceptable from a medication error perspective. We do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sutab received on March 11, 2020 from Braintree.

Table 2. Relevant Product Information for Sutab	
Initial Approval Date	N/A
Active Ingredient	sodium sulfate, magnesium sulfate, and potassium chloride
Indication	For cleansing of the colon in preparation for colonoscopy in adults.
Route of Administration	oral
Dosage Form	tablets
Strength	1.479 g, 0.225 g, and 0.188 g per tablet
Dose and Frequency	Administration of two doses of SUTAB (24 tablets) are required for a complete preparation for colonoscopy. Twelve (12) tablets are equivalent to one dose. <u>Dose 1 – On the day prior to colonoscopy:</u> • A low residue breakfast may be consumed. Examples of low residue foods are eggs, white bread, cottage cheese, yogurt, grits, coffee, tea. • After breakfast, only clear liquids may be consumed until after the colonoscopy. • Early in the evening prior to colonoscopy, open one bottle of 12 tablets. • Fill the provided container with 16 ounces of water (up to the fill line). Swallow each tablet with a sip of water and drink the entire amount over 15 to 20 minutes. • Approximately one hour after the last tablet is ingested, fill the provided container a second time with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • Approximately 30 minutes after finishing the second container of water, fill the provided container again with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • If patients experience preparation-related symptoms (e.g. nausea, bloating, cramping), pause or slow the rate of drinking the additional water until symptoms diminish.

	<u>Dose 2 - Day of colonoscopy:</u> • Continue to consume only clear liquids until after the colonoscopy. • The morning of colonoscopy (5 to 8 hours prior to the colonoscopy and no sooner than 4 hours from starting Dose 1), open the second bottle of 12 tablets. • Fill the provided container with 16 ounces of water (up to the fill line). Swallow each tablet with a sip of water and drink the entire amount over 15 to 20 minutes. • Approximately one hour after the last tablet is ingested, fill the provided container a second time with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • Approximately 30 minutes after finishing the second container of water, fill the provided container again with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • If patients experience preparation-related symptoms (e.g. nausea, bloating, cramping), pause or slow the rate of drinking the additional water until symptoms diminish. • Complete all SUTAB tablets and water at least two hours prior to colonoscopy.
How Supplied	Two bottles, each bottle contains 12 tablets. One container with a 16-ounce fill line.
Storage	Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 1, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, "Sutab". Our search identified three previous reviews[a,b,c], and we confirmed that our previous recommendations were implemented.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Sutab labels and labeling submitted by Braintree.

- Container label received on May 12, 2020
- Carton labeling received on May 12, 2020
- Prescribing Information (Image not shown) received on March 11, 2020, available from \\CDSESUB1\evsprod\nda213135\0032\m1\us\sutab-draft-labeling-text-version-2-clean.docx

G.2 Label and Labeling Images

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[a] Vee, S. Label and Labeling Review for Sutab (NDA 213135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 08. RCM No.: 2019-1052.

[b] Vee, S. Label and Labeling Review for Sutab (NDA 213135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 21. RCM No.: 2019-1052-1.

[c] Vee, S. Label and Labeling Review for Sutab (NDA 213135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 13. RCM No.: 2019-1052-2.

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH K VEE
09/08/2020 10:05:17 AM

IDALIA E RYCHLIK
09/08/2020 11:18:50 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 5, 2020
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213135
Product Name and Strength:	Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, 1.479 g/0.225 g/0.188 g
Applicant/Sponsor Name:	Braintree
OSE RCM #:	2019-1052-3
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on March 3, 2020 for Sutab. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised carton labeling for Sutab (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to an information request from DGIEP where revisions to prescribing information (PI) and medication guide were sent to the Applicant on February 25, 2020. The revisions to the carton labeling were made to be consistent with the PI.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

SARAH K VEE
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03/05/2020 11:58:30 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	Date February 6, 2020
To:	Andrew Kelleher, PhD, MS Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 213135
Applicant:	Braintree Laboratories, Inc.

1 INTRODUCTION

On May 15, 2019, Braintree Laboratories, Inc. submitted for the Agency's review a New Drug Application (NDA) for SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, for oral use. SUTAB is an osmotic laxative with a proposed indication for cleansing of the colon in preparation for colonoscopy in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on May 31, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, for oral use.

DMPP conferred with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on January 13, 2020.

2 MATERIAL REVIEWED

- Draft SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, for oral use MG and IFU received on May 15, 2019, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on January 22, 2020.
- Draft SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, for oral use Prescribing Information (PI) received on May 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 22, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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LASHAWN M GRIFFITHS
02/07/2020 08:45:21 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 29, 2020

To: Andrew Kelleher, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for SUTAB (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, for oral use

NDA: 213135

In response to DGIEP's consult request dated May 31, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA for SUTAB.

PI and Medication Guide/IFU carton panels: OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail from DGIEP on January 22, 2020.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide/IFU carton panels will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton panels (not including the IFU panels) and container labeling submitted by the Sponsor, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
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Clinical Inspection Summary

Date	January 9, 2020
From	Zana Marks, M.D, M.P.H., OSI Reviewer Aisha Johnson, MD, MPH, MBA, Acting TL Kassa Ayalew, M.D., M.P.H., Branch Chief Office of Scientific Investigations/GCPAB
To	Omolara Adewuni M.D. Tara Altepeter, M.D. Andrew Kelleher, RPM Division of Gastroenterology and Inborn Errors Products (DGIEP)
NDA #	213135
Applicant	Braintree Laboratories, Inc.
Drug	Sodium Sulfate, Magnesium Sulfate, Potassium Chloride
NME (Yes/No)	No
Therapeutic Classification	Osmotic Bowel Cleansing (Preparation)
Proposed Indication(s)	BLI4700 (Oral Sulfate Tablets) is proposed for use as a bowel cleansing agent as preparation for colonoscopy
Consultation Request Date	June 29, 2019
Summary Goal Date	January 20, 2020
Action Goal Date	March 15, 2020
PDUFA Date	March 15, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Moussa, Rausher, Lowe, Korman, Gross, and Rex were inspected in support of NDA 213135.

The study site of Dr. Louis Korman (Site 112) was issued a Form FDA 483 for failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Dr Korman's written response to the FDA Form 483 included a corrective action plan that appears reasonable.

The study data derived from the clinical investigator inspections, including Dr. Korman, are considered reliable.

II. BACKGROUND

The sponsor submitted this NDA for BLI4700 (Oral Sulfate Tablets) with the proposed indication for use as a bowel cleansing agent as a preparation for colonoscopy. Sulfates are poorly absorbed, and they remain in the lumen of the gastrointestinal tract where they exert an

osmotic effect. The sponsor claims that the osmotic activity of BLI4700 increases the water content of stool and promotes a bowel movement. Because this product is supplied in tablet form, the sponsor proposes their product will be more acceptable than currently available liquid bowel preparations.

Two similar Phase 3 studies in adult subjects requiring colonoscopy for a routinely accepted indication (screening and diagnostic) were conducted in support of this New Drug Application. Study BLI4700-301 was a single-blind, multicenter study that evaluated split-dose (PM/AM) administration of BLI4700 tablets compared to MoviPrep. Study BLI4700-302 was a single-blind, multicenter study that evaluated split-dose (PM/AM) administration of BLI4700 tablets compared to Prepopik.

Summary of Protocol BLI4700-301

Study Design: Multicenter, parallel-group, single-blind, active-controlled

Primary Endpoint:

Overall preparation success or failure after completion of the examination.
Investigators graded each preparation on a scale from 1 to 4:

- 1 (poor) or 2 (fair) equal failure
- 3 (good) to 4 (excellent) equal success

Protocol BLI4700-301 entitled, “A Safety and Efficacy Comparison of BLI4700 Bowel Preparation versus an FDA-approved Comparator in Adult Subjects prior to Colonoscopy” was conducted from January 11, 2018 to July 10, 2018 and enrolled 620 subjects at 22 sites in the U.S. The primary objective of this study was to compare the safety and efficacy of BLI4700 colon prep tablets to MoviPrep as bowel preparation prior to colonoscopy in adult patients.

The study consisted of a screening visit (Visit 1). Subjects who met the eligibility criteria during the screening visit were assigned to receive either BLI4700 or MoviPrep using a dynamic minimization scheme. In this scheme, subjects are assigned to a group and then assigned the treatment group by the IWRS.

Group 1: Subjects who meet any of the following criteria:

- Prior diagnosis of constipation (historical or active)
- History of prior failed bowel preparation (inadequate examination)
- Currently taking opioid medications
- Body Mass Index > 35

Group 2: Subjects scheduled for a colonoscopy 12:00 PM or later

Group 3: Subjects not meeting Group 1 or 2 criteria

Unblinded participants included the subjects and the study personnel who dispensed test article, processed the drug returns, and accounted for drug accountability. Colonoscopy occurred at Visit 2. There was a follow-up visit (Visit 3 at 24 to 48 hours post colonoscopy)and

a follow-up phone call at Day 30 for subjects that had abnormal laboratory values. Subjects that had laboratory or EKG abnormalities were seen at Visit 4-Day 7 and Visit 5-Day 30.

The primary efficacy endpoint for these studies was overall preparation success or failure after completion of the colonoscopy examination. Blinded endoscopists graded each preparation on a four-point scale.

Table 1 Colonoscopy Scoring System

Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional bowel preparation required.
2	Fair	Enough feces even after washing and suctioning to prevent clear visualization of the entire colonic mucosa.
3	Good	Feces and fluid requiring washing and suctioning, but still achieves clear visualization of the entire colonic mucosa.
4	Excellent	No more than small bits of feces/fluid which can be suctioned easily; achieves clear visualization of the entire colonic mucosa.

Preparation success was defined as overall cleansing assessment by the colonoscopist of "Excellent" (score = 4) or "Good" (score = 3). A failed preparation was defined as overall cleansing assessment of "Fair" (score = 2) or "Poor" (score = 1) as well as subjects who did not have a colonoscopy due to intolerance or the Investigator's assessment of inadequate cleansing as well as cleaning inadequate for evaluation.

Investigators planning to perform colonoscopies were required to view the cleansing scale training video at the start of the study prior to performing any procedures and were also required to view the video a second time after approximately 50% of the planned colonoscopies in the study had been performed.

As outlined in the "Statistical Analysis Plan (SAP) for Central Reading of Colonoscopies" (Item #4 in the background package), the first four colonoscopy videos received from each study site were submitted for central review. The intent of this review was to confirm that the sites were recording the colonoscopies correctly and to evaluate agreement between the local and central readers at a time early enough in the study to allow for retraining of colonoscopists if necessary.

Summary of Protocol BLI4700-302
Study Design: Multicenter, parallel-group, single-blind, active-controlled
Primary Endpoint:
Overall preparation success or failure after completion of the examination.
Investigators graded each preparation on a scale from 1 to 4:

- 1 (poor) or 2 (fair) equal failure and
- 3 (good) to 4 (excellent) equal success

Protocol BLI4700-302 entitled, "A Safety and Efficacy Comparison of BLI4700 Bowel Preparation versus an FDA-approved Comparator in Adult Subjects prior to Colonoscopy" was conducted from August 8, 2017 to March 26, 2018 and enrolled 455 subjects at 20 sites in the U.S. The primary objective of this study was to compare the safety and efficacy of BLI4700 colon prep tablets to Prepopik as bowel preparation prior to colonoscopy in adult patients.

Except for the comparator, this trial was similar to BLI4700-301. See above for the clinical trial details.

III. RESULTS (by site):

1. **Louis Korman, M.D., Site # 112, Protocol # BLI4700-302**
   MGG Group Co., Inc., Chevy Chase Clinical Research, 5550 Friendship Blvd., Ste T90
   Chevy Chase, MD 20815-7313

Inspection dates: November 4-11, 2019, 11/13/2019.

At this site, 59 subjects were consented and screened, 57 subjects were enrolled, 43 subjects completed the study, 11 subjects withdrew consent, three (3) subjects were lost to follow-up, and two (2) were screen failures.

The inspection included, but was not limited to, the review of subject's case histories, which covered Informed Consent Forms (ICFs), Case Report Forms (CRFs), laboratory reports, medical records, and subject questionnaires. Source documents were compared against the eCRFs and data listings provided with the assignment. Study records reviewed included drug accountability records, site correspondence with the sponsor, monitor and Institutional Review Board (IRB); regulatory records, including FDA 1572s and financial disclosure records.

At the close of the inspection, a one-item Form FDA-483, Inspectional Observations, was issued to Dr. Korman. The one-item observation listed on the FDA 483 was as follows: failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, review of the source documents revealed:

a. 31 out of 57 subjects received Propofol, Lidocaine, and/or fentanyl as observed on each subject's Visit 2 (Colonoscopy) Source Document however, the medications did not appear on the eCRF nor the data listing provided to the FDA.
   i. The following subjects received the sedative drug Propofol during their colonoscopy: Subject # (b) (6)
   ii. The following subjects received the sedative drugs Propofol and Lidocaine during their colonoscopy: Subject (b) (6)
   iii. The following subject received the sedative drugs Propofol, Lidocaine, and Fentanyl during his/her colonoscopy: Subject # (b) (6)

   OSI Reviewer Comment: Failure to accurately document medications administered for sedation in the eCRF potentially undermines the reliability of data obtained from this site. The number of subjects where this important information was omitted suggests that site personnel may not have received appropriate training with regard to documenting and recording the use of the sedative drugs in the endoscopy center chart as well as the eCRF, which was required by the protocol. Although the clinical investigator failed to properly document and report medications administered for sedation to the sponsor, omission of sedative documentation in the eCRFs does not appear to have clinical significance on the procedures performed and patient safety and efficacy assessment.

b. Five out of 59 subjects screened had discrepancies with their reported Patient Status.
   i. (b) (6): source document titled, "PATIENT STATUS", signed by PI on (b) (6) and the eCRF indicates "Withdrawal of Consent by Subject" and a Note to File dated (b) (6), indicates subject was a "Screen Failure Post Randomization".
   ii. (b) (6): source document titled, "PATIENT STATUS", signed by PI on (b) (6) indicates "Subject was a Screen Failure" and the eCRF indicates "Subject Was a Screen Failure Post Randomization".
   iii. (b) (6): source document titled, PATIENT STATUS", signed by PI on (b) (6) and the eCRF indicates "Withdrawal of Consent by Subject" and a Note to File dated (b) (6), indicates subject was a "Screen Failure Due to Lack of Availability".
   iv. (b) (6): source document titled, "Patient STATUS", signed by PI on (b) (6) and eCRF indicates subject completed the study on (b) (6), however, there are two Note to Files. Notes to File dated (b) (6), indicates subject did not complete Visit 5 and several attempts were made, but unsuccessful and subject was "Discontinued".

v. (b) (6): source document titled, PATIENT STATUS", signed by PI on (b) (6), indicates "Subject Was a Screen Failure" and the eCRF indicates "Subject Was a Screen Failure Post Randomization".

OSI Reviewer Comment: Although this patient was discontinued post-randomization, the patient did not receive the study drug. Therefore, this infraction bore no clinical significance and does not impact the reliability of the data

c. Subject (b) (6): was screened and consented on (b) (6). Progress Notes for Visit 2 and protocol deviation indicates "subject did not complete Visit 2 Colonoscopy, visit was scheduled for (b) (6) however, the colonoscopy was completed using another IP outside of the study". The eCRF and the source document, titled "Patient Status", signed by the PI on (b) (6) indicates subject completed the study (b) (6). Per the Section 3.5.2 of Protocol #BLI4700-302, "Subjects who have participated in an investigational surgical, drug, or device study within the past day" are ineligible subjects.

OSI Reviewer Comment: This study documentation error emphasizes the site's need for better administrative oversight and support to site personnel providing documentation and the research coordinators. This finding appears to be isolated in nature, and it is unlikely that it would affect patient safety or data reliability.

d. Subject (b) (6): Source document indicates Visit 1 was conducted (b) (6). Review of the laboratory samples indicates the samples were not collected until (b) (6) however, the Visit 1 source document indicates the samples were collected (b) (6). Per the protocol visit schedule, laboratory samples were to be collected at Visits 1, 2, and 3.

OSI Reviewer Comment: The violation was reported as a deviation. This observation appears to be isolated and does not appear to represent a systemic issue at the site.

e. Review of subject records revealed various incomplete and missing source documents. For example:
   i. (b) (6): missing Patient Status Sheet.
   ii. (b) (6): page 1 of source document for Visit 3 is incomplete.

OSI Reviewer Comment: None of the incomplete documents described above created data reliability issues or proved clinically relevant.

There were two items discussed during Dr Korman's close-out meeting as well. The door to the investigational products (IP) storage area was propped open with a trashcan. The door, usually locked, was propped open to allow staff to pass back and forth to gather products for subjects in an active study. Dr Korman stated that he would speak to the clinical staff and make sure the door remained closed and locked when not in use. The second discussion item involved the firm's failure to maintain all correspondences between the site and the sponsor in the regulatory binder which was maintained by the Manger of Operations (MOO). When queried by the inspector, the MOO responded that the majority of the correspondence was

held between the sponsor and the clinical research coordinator who is no longer employed by CCCR. As such, they are not able to retrieve related correspondence.

Reviewer's Comment(s): *Dr Korman responded to the Form FDA-483 Inspectional Observations and the discussion items in a document dated November 27, 2019. Corrective actions were delineated and included the following: Specific training for recording of concomitant medications in the appropriate locations according to the protocol were reviewed and are now implemented as part of the facility's Documentation Procedures. The inspection site group reviewed and identified the need to include Notes to File defining the conditions of patient withdrawal, screen failure or other events that might be considered protocol deviations.*

Additionally, based on inspection concerns, the group identified the need for expanded administrative support and expanded to include a designated delegated employee whose role is to support the documentation needs of the studies and the research coordinators.
The Director and Principle Investigator will review and monitor all proposed studies to appropriately match resources and requirements both prior to and during the studies. The site implemented the resource evaluation process as part of their Research Procedures.
The observations appear to be isolated incidents that do not appear to represent systemic issues at this site. The corrective actions implemented at the site appear reasonable.

2. Sam Moussa, M.D., Site # 204, Protocol # BLI4700-301
2585 N Wyatt Drive, Adobe Clinical Research, LLC
Tucson, Arizona, 85712-6104

Inspection dates: November 18-21, 2019.

At this site, 66 subjects were consented and screened, 62 subjects were enrolled and completed the study. All primary data endpoints were verifiable and available for review in the source records and eCRFs at the firm. The Global Cleansing Assessment (i.e., Overall Cleansing Assessment) scores were completed and matched scores documented in the source record for 62 subjects against the data listings provided in the background materials for the study. No discrepancies were noted.

For this inspection, a complete review of regulatory documentation at the study site was performed. The study protocol signed investigator agreements, financial disclosure statements, IRB approvals and site submissions to the IRB and the sponsor were reviewed. The correspondence, monitoring reports, subject case history files, informed consent forms, subject visits and assessments, case report forms, subject diary data, test article accountability and subject adverse events were also reviewed. There was no under reporting of adverse events.

In general, this clinical site appeared to be following Good Clinical Practice. No significant inspectional observations were observed during this inspection. A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection

3. Douglas K. Rex, M.D., Site # 134, Protocol #BLI4700-301

IU Health University Hospital
550 University Boulevard
Indianapolis, IN 46202-5149

Inspection Dates: October 18-22, 2019

At this site 38 subjects were screened and enrolled and 34 subjects completed the study. There were 2 screen failures and 2 withdrawals. The following operations were verified during the inspection: protocol adherence, ensuring informed consent was appropriately obtained for each subject, verification of 1572s and financial disclosures. Ensured subjects met study eligibility criteria, randomization, concomitant medications, protocol deviations, ensured article accountability/disposition, ensured source documents and CRFs were consistent with the data listings.

The efficacy endpoint data was verifiable. There appeared to be no under-reporting of adverse events.

In general, this clinical site appeared to be following Good Clinical Practice. No significant inspectional observations were observed during this inspection. A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection

4. Craig G. Gross, M.D., Site# 117, Protocol # BLI4700-302
Del Sol Research Management LLC
5700 E Pima Street, Ste A
Tucson, Arizona, 85712-5637

Inspection Dates: November 4-7, 2019

At this site 64 subjects were consented and screened. There were 14 subjects who were screen failures and /or were terminated early. Seven subjects were lost to follow-up and43 subjects completed the study.

Review of study-related records for 30 subjects showed source records were attributable, legible, contemporaneous, original, accurate and complete. All study assessments were completed as outlined in the study protocol with no notable exceptions.

All primary data endpoints were verifiable and available for review in the source records and eCRFs at the firm. The inspector verified the Global Cleansing Assessment (i.e., Overall Cleansing Assessment) scores were completed and matched scores documented in the source record for 32 subjects against the data listings provided in the background materials for the study. No discrepancies were noted. There appeared to be no under-reporting of adverse events.

In general, this clinical site appeared to be following Good Clinical Practice. No significant inspectional observations were observed during this inspection. A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection

5. John E. Lowe, M.D., Site# 217, Protocol # BLI4700-301
5896 S. Ridgeline Drive,

Six subjects screen failed after randomization and did not take any of the study drug due to the following: three withdrew consent, two had low potassium at visit 1 that met exclusion criteria, and one had high potassium at visit 1 that met exclusion criteria.

A total of 62 subjects took the study drug, and 61 subjects had a colonoscopy after taking study drug. One subject had an inadequate colonoscopy preparation, and a colonoscopy was not performed in that subject. Sixty-one subjects completed the study. One subject was lost to follow up after the colonoscopy visit 2. During this inspection, the inspector reviewed complete study records for 25 subjects in the BLI4700 study, and ICFs for 68 subjects.

The inspector reviewed source documents which consisted of paper CRFs, colonoscopy procedure notes, colonoscopy nurse's notes, paper subject diaries documenting dietary and study drug compliance, colonoscopy videos (on USB thumb drive), laboratory reports, and IWRS printed email confirmations (of randomization and study visits). The nurse's notes covering the colonoscopies, including sedation medication, vital signs, and ECG strips, were not maintained with the study records. However, the nurse's notes for the colonoscopies were provided and compared to the study coordinators' documentation. No data discrepancies were observed.

For 25 subjects, the inspector compared source documentation to the data listings provided with the assignment and verified, for the reviewed subjects, all source documentation matched the data listings regarding the primary efficacy endpoint, randomization, subject discontinuations, and concomitant medications. Protocol deviations that were not in the data listing, but which were adequately documented in the source documentation, including minor issues with study drug compliance, dietary restrictions, and out of window visit were observed. There appeared to be no evidence of under-reporting of adverse events. The observations appear to be isolated incidents that do not appear to represent systemic issues at this site.

In general, this clinical site appeared to be following Good Clinical Practice. No significant inspectional observations were observed during this inspection. A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection.

6. David B. Rausher, M.D., Site# 215, Protocol # BLI4700-301
2665 N Decatur Road, Ste 550
Decatur, Georgia, 30033-6146

Inspection Dates: October 28- November 1, 2019

Subject participation at this site consisted of 57 consented subjects, one of which was a screen failure. A total of 50 subjects completed the study and 6 subjects discontinued early. The

inspection included, but was not limited to, a review of records including informed consent forms (ICFs), subject records, colonoscopy records, laboratory records, drug accountability records, financial disclosure documents and training records.

All primary data endpoints were verifiable and available for review in the source records and eCRFs at the firm. There appeared to be no under-reporting of adverse events.

In general, this clinical site appeared to be following Good Clinical Practice. No significant inspectional observations were observed during this inspection. A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection.

{See appended electronic signature page}

Zana H. Marks, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CC:

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Review Division /Medical Team Leader/Tara Altepeter
Review Division /Project Manager/Kelly Richards
Review Division/MO/ Marjorie Dannis
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Aisha Johnson
OSI/DCCE/GCP Reviewer/ Zana Marks
OSI/ GCP Program Analysts/ Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

ZANA H MARKS
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AISHA P JOHNSON
01/17/2020 01:21:38 PM

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01/17/2020 02:13:28 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 13, 2020
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213135
Product Name and Strength:	Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, 1.479 g/0.225 g/0.188 g
Applicant/Sponsor Name:	Braintree
OSE RCM #:	2019-1052-2
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 6, 2020 for Sutab. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container label and carton labeling for Sutab (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Vee S. Label and Labeling Review for Sutab (NDA 213135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 21. RCM No.: 2019-1052.

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/s/

SARAH K VEE
01/13/2020 09:19:54 AM

ASHLEIGH V LOWERY
01/13/2020 10:05:59 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 21, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213135
Product Name and Strength:	Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, 1.479 g/0.225 g/0.188 g
Applicant/Sponsor Name:	Braintree
OSE RCM #:	2019-1052-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 8, 2019 for Sutab. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container label and carton labeling for Sutab (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. The revision to the preparation procedure on the carton labeling does not match the prescribing information and the strength statement can be revised to improve readability.

3 RECOMMENDATIONS FOR BRAINTREE

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Label and Carton Labeling)

[a] Vee S. Label and Labeling Review for Sutab (NDA 213135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 08. RCM No.: 2019-1052.

a. To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 1.479 g instead of 1.479g) for all instances of the strength statement.

B. Carton Panel #3 (Preparation Procedure)

a. Under Step 2: Please revise Step 2, second sentence, to match the prescribing information to read, "Swallow each tablet with a sip of water and drink the entire [redacted] (b) (4) over 15 to 20 minutes".

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/s/

SARAH K VEE
11/21/2019 01:38:55 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: November 14, 2019 **Date Consulted:** June 6, 2019

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

To: Andrew Kelleher, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Error Products (DGIEP)

Drug: Sutab (sodium sulfate, magnesium sulfate, potassium chloride) tablets

NDA: 213135

Proposed Indication: An osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.

Applicant: Braintree Laboratories, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 213135 submitted on May 15, 2019
- DPMH Review of Plenvu (PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride, and potassium chloride) by Jane Liedtka, MD, dated November 14, 2017, DARRTS Reference ID: 4180957.[1]

Consult Question: DGEIP requests review of PLLR labeling for this new NDA

[1] The DPMH Review of Plenvu was part of the materials reviewed for background purposes but was not a source relied upon for the labeling recommendations below.

INTRODUCTION

On May 15, 2019, the applicant, Braintree Laboratories, Inc., submitted an original new drug application (NDA) for Sutab (oral sodium sulfate, magnesium sulfate, potassium chloride) tablets via the 505(b)(2) regulatory pathway. On June 6, 2019, the Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy*, *Lactation,* and *Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- Sutab (oral sodium sulfate, magnesium sulfate, potassium chloride) tablets is an osmotic laxative with a proposed indication for cleansing of the colon in preparation for colonoscopy in adults.
- Sutab is relying on nonclinical and clinical data from Suprep NDA 022372 (also owned by the applicant) for this 505(b)(2) application. Suprep was initially approved for marketing in the US in 2010 as an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.
- Sutab shares the same active ingredients as Suprep with the exception of potassium chloride instead of potassium sulfate. Sutab is a tablet and Suprep is an oral solution.

Sutab Drug Characteristics[2]

- *Drug Class:* osmotic laxative
- *Mechanism of action (MOA):* (b) (4)
- *Pharmacodynamics:* (b) (4)
- *Description:* Sutab contains two bottles, each with 12 tablets. Each tablet dose contains: sodium sulfate 17.75 grams, magnesium sulfate 2.7 grams, potassium chloride 2.25 grams. Molecular weight: sodium sulfate (142.04 Daltons), magnesium sulfate (120.37 Daltons), potassium chloride (74.55 Daltons).
- *Dosage and administration:* split dose (2-day) regimen. The evening before colonoscopy take 1 bottle of tablets (12 total) while drinking 16 oz of water followed by an additional 16 oz of water 1 hour later and a third 16 oz of water 30 minutes after finishing the previous container of water. The day of colonoscopy repeat all steps using the second bottle of tablets. Complete the preparation and water at least 2 hours before colonoscopy.
- *Adverse reactions:* nausea, abdominal distension, vomiting, abdominal pain, (b) (4)

Reviewer's Comment

The applicant's proposed labeling states (b) (4) *However, in DPMH's discussion with the Clinical Pharmacology Review Team, the reviewers stated that they do not agree with the applicant's conclusions* (b) (4)

[2] Sutab (N213135) proposed prescribing information

REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies have not been conducted with Sutab.

Applicant's Review of Pharmacovigilance Database

There is no pharmacovigilance data for Sutab (as it has not yet been approved for marketing), however, the applicant provided drug utilization and pharmacovigilance data for Suprep.

Drug Utilization: Since approval on August 5, 2010 through March 31, 2019, a total of (b) (4) Suprep Bowel Prep Kits have been distributed. A review of the pharmacovigilance database was performed (as applicable based on reports where age was provided) for females of reproductive age (defined as age 15-44) which yielded Suprep Bowel Prep Kits exposure to 283 females of reproductive potential.

Pharmacovigilance: Since approval of Suprep Bowel Prep Kit on August 5, 2010 through March 31, 2019, a total of 3,747 adverse events have been reported. Of all 3,747 reports, only 1 reporter indicated a positive pregnancy test on the day of the planned colonoscopy procedure which was cancelled. The patient was subsequently found to no longer be pregnant by ultrasound that showed no fetus or yolk sac. No additional information is available.

Applicant's Review of Published Literature

The applicant performed a search in PubMed specific to the components of the listed drug relied upon Suprep (oral sodium sulfate, magnesium sulfate, potassium sulfate). Search terms included "magnesium sulfate" OR" sodium sulfate" OR "potassium sulfate" OR "oral sulfate solution" OR "Suprep" AND "pregnant" OR "pregnancy."

None of the abstracts resulting from this search discussed the use of SUPREP or an oral sulfate during pregnancy. Therefore, the applicant concluded there is no relevant published literature related to the use of Suprep or it's oral components during pregnancy. However, the applicant did note that there is a substantial amount of published literature related to the use of intravenous and intramuscularly administered magnesium sulfate for the treatment of pregnancy related conditions including pre-eclampsia, preterm labor, and as a neuroprotective agent to reduce the incidence of cerebral palsy in preterm neonates.[3,4,5,6,7]

Reviewer's Comment

The applicant further noted that the available literature on the use of intravenous magnesium sulfate during pregnancy indicates that maternal blood levels of magnesium were substantially increased by this therapy. However, in clinical studies BLI800-301 and 302 for

[3] Amaral LM, Wallace K, Owens M, LaMarca B. Pathophysiology and Current Clinical Management of Preeclampsia. Curr Hypertens Rep. 2017 Aug;19(8):61.

[4] Chollat C, Marret S. Magnesium sulfate and fetal neuroprotection: overview of clinical evidence. Neural Regen Res. 2018 Dec;13(12):2044-2049.

[5] Euser et al. Magnesium sulfate for the treatment of eclampsia: a brief review. Stroke. 2009 Apr;40(4):1169-75.

[6] Rundell K et al. Preterm Labor: Prevention and Management. Am Fam Physician. 2017 Mar 15;95(6):366-372.

[7] Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection: A Meta-analysis Based on PRISMA Guidelines. Medicine (Baltimore). 2016 Jan;95(1):e2451.

Suprep (the listed drug relied upon), subjects showed no elevation of their magnesium levels suggesting that the poor oral bioavailability of magnesium limits circulating levels in subjects receiving Suprep. This Reviewer agrees with the applicant's conclusions that "these data indirectly indicate that short term exposure to one of the key salts found in Suprep and Sutab (oral magnesium sulfate) would not likely produce a safety hazard for pregnant or lactating patients."

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[8], TERIS[9], Reprotox[10], and Briggs[11] to find relevant articles not cited by the applicant. Search terms included "oral sodium sulfate," "oral magnesium sulfate", "oral potassium chloride" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," or "miscarriage."

- No additional relevant articles were identified in **PubMed** or **Embase**.

Oral Magnesium Sulfate

- **Briggs** pregnancy recommendation for magnesium sulfate is "compatible." The authors notes magnesium sulfate is commonly used as an anticonvulsant for toxemia (pre-eclampsia) and as a tocolytic agent for premature labor during the last half of pregnancy. "No reports linking the use of magnesium sulfate with congenital defects have been located."

Oral Potassium Chloride

- **Briggs** pregnancy recommendation for potassium chloride is "compatible." The author notes potassium chloride is a natural constituent of human tissues and fluids.
    - In a surveillance study[12] of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 35 newborns had been exposed to oral potassium salts during the 1st trimester. One (2.9%) infant with major birth defects was observed (one expected), a case of limb reduction and hypospadias.

Oral Sodium Sulfate

- This Reviewer did not identify any citations for oral sodium sulfate use in pregnancy.

LACTATION

Nonclinical Experience

Animal lactation studies have not been performed with Sutab.

[8]Truven Health Analytics information, http://www.micromedexsolutions.com, Accessed 10/31/19.
[9]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 10/31/19.
[10]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/31/19
[11] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 9th Ed. 2011.
[12] F. Rosa, personal communication, FDA, 1993.

Applicant's Review of Published Literature

The applicant performed a search in PubMed specific to the components of the listed drug relied upon Suprep (oral sodium sulfate, magnesium sulfate, potassium sulfate). Search terms included "magnesium sulfate," " sodium sulfate," "potassium sulfate," "oral sulfate solution" OR "Suprep" AND "lactating" OR "lactation."

No relevant published literature was identified that described the use of Suprep or oral sulfates during lactation. The applicant noted there are published literature available related to the use of intravenous magnesium sulfate during the immediate postpartum period in pre-eclamptic women which suggest the breastfed infant of a treated mother would receive only 1.5 mg of magnesium more than the infant of a non-treated mother.[13] Further, the American Academy of Pediatrics has identified magnesium sulfate as compatible with breastfeeding.[14]

DPMH's Review of Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*[15], LactMed[16], Micromedex[8], Reprotox[10], Briggs[11], PubMed, and Embase using the terms "oral sodium sulfate," "oral magnesium sulfate," OR "oral potassium chloride" AND "lactation" OR "breastfeeding."

- No additional relevant publications were identified in **PubMed** or **Embase.**

- In *Medications and Mother's Milk*, the author, Thomas Hale, classifies the general use of osmotic laxatives during breastfeeding as "L2-no data-probably compatible" because they are poorly absorbed, largely stay in the gastrointestinal tract, and are eliminated without significant systemic absorption. The author notes "while we do not have specific data on the use of higher doses of oral magnesium salts or of the phosphates, the lactocyte controls the microelectrolyte concentrations of milk closely. Minute changes in maternal levels which could potentially occur following the use of these laxatives, would not likely alter milk content of these electrolytes."

Oral Magnesium Sulfate

- **Briggs** breastfeeding recommendation for magnesium sulfate is "compatible." The author notes magnesium salts may be encountered by nursing mothers using over-the-counter laxatives. A study of 50 mothers who received an emulsion of magnesium and liquid petrolatum or mineral oil found no evidence of changes or frequency of infant stools.[17]

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[13] Cruikshank DP, Pitkin RM, Reynolds WA, Williams GA, Hargis GK Effects of magnesium sulfate treatment on perinatal calcium metabolism. I. Maternal and fetal responses. Am J Obstet Gynecol. 1979 Jun 1;134(3):243-9.
[14] American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001 Sep;108(3):776-89.
[15] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.
[16] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 2/13/19
[17] Baldwin WF. Clinical study of senna administration to nursing mothers: assessment of effects on infant bowel habits. CMAJ 1963;89:566-8.

- *Medication and Mother's Milk* classifies the use of magnesium sulfate during breastfeeding as "L1-limited data-compatible." The author notes magnesium is a normal plasma electrolyte and is used pre and postnatally in women with pre-eclampsia.
    - In a lactation study[18] of 10 pre-eclamptic patients who received magnesium at 4 gram IV loading dose followed by 1 gram per hour IV for more than 24 hours, the average milk magnesium levels in treated subjects were 6.4 mg/dL, only slightly higher than untreated controls which were 4.77 mg/dL. On day 2, the average milk magnesium levels in treated groups were 3.83 mg/dL, which was not significantly different from untreated controls, 3.19 mg/dL. By day 3, the treated and control groups breastmilk levels were identical (3.54 vs 3.52 mg/dL). The mean maternal serum magnesium level on day 1 in the treated group was 3.55 mg/dL, which was significantly higher than untreated controls, 1.82 mg/dL. In both treated and control subjects, levels of milk magnesium were approximately twice those of maternal serum magnesium levels, with the milk-to-serum ratio being 1.9 in treated subjects and 2.1 in control subjects. "This study clearly indicates a normal concentrating mechanism for magnesium in human milk. It is well known that oral magnesium absorption is very poor, averaging only 4%.[19] Further, this study indicates in treated groups, infants would only receive about 1.5 mg of oral magnesium more than the untreated controls. It is very unlikely that the amount of magnesium in breastmilk would be clinically relevant."

Oral Potassium Chloride

- **Briggs** breastfeeding recommendation for potassium chloride is "compatible." The author notes that breast milk is naturally high in potassium with levels that are 3-4 times those in plasma.[20] The concentration of potassium in mature milk is about 55-57 mg/dL (about 14-15 mEq/L). "Because potassium freely passes into and out of milk, the use of potassium chloride by a lactating woman with normal plasma potassium levels would have no adverse effect on a nursing infant."

- *Medications in Mother's Milk* classifies potassium salts (including potassium chloride) as "L3-no data-probably compatible." The author notes potassium is a mineral commonly found in many foods. The level of potassium in breastmilk is between 9-14 mEq/L.[21] Potassium levels in breastmilk do not appear to increase with potassium supplement."

Oral Sodium Sulfate

- This Reviewer did not identify any citations for oral sodium sulfate use in lactation.

[18] Cruikshank DP, et al. Breast milk magnesium and calcium concentrations following magnesium sulfate treatment. AJOG 1982;143(6):685-688.
[19] Morris ME, et al. Absorption of magnesium from orally administered magnesium sulfate in man. J Toxicol Clin Toxicol 1987; 25:371-82.
[20] Lawrence RA, et al. Biochemistry of human milk. In Breastfeeding. A Guide for the Medical Profession. 5th ed. St. Lous, MO: Mosby, 1999:127-9.
[21] Finley DA, et al. Inorganic constituents of breast milk from vegetarian and nonvegetarian women: relationships with each other and with other organic constituents. J Nutr. 1985 Jun; 115(6):772-81.

Reviewer's Comment
This reviewer notes that several of the components of Sutab are naturally present in human milk including sodium, magnesium, potassium, chloride, and sulfate.[22] However, there are no available data on Sutab use during lactation.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal fertility studies have not been conducted with Sutab.

Applicant's Review of Published Literature

The applicant performed a literature search in PubMed using the search terms "sulfate" and "fertility" on February 21, 2019. No relevant articles were identified that discussed the use of Suprep or oral sulfate solution and effects on fertility.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox[10] using the terms "oral sodium sulfate," "oral magnesium sulfate", OR "oral potassium chloride" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION and CONCLUSIONS

Pregnancy

There are no available data regarding the use of Sutab during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Sutab. As noted above, DPMH discussed the amount of systemic absorption of Sutab with the Clinical Pharmacology Review Team who does not agree with the applicant's conclusion (b) (4) . Therefore, DPMH recommends subsection 8.1 of Sutab labeling include a Risk Summary statement that reflects the lack of available clinical and nonclinical data on Sutab use during pregnancy.

Lactation

There are no available data specific to the use of Sutab during lactation including the presence in human or animal milk, the effects on the breastfed infant, or the effects on milk production. However, DPMH notes that several of the components of Sutab are naturally present in human milk (including potassium, chloride, magnesium, sodium, and sulfate). Therefore, DPMH recommends subsection 8.2 of Sutab labeling include the following risk/benefit statement, "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sutab and any potential adverse effects on the breastfed infant from Sutab or from the underlying maternal condition."

DPMH considered whether a lactation study should be required for Sutab. Considering the anticipated use mostly in older adults (median age of patients in Study 1 was 60 years and Study 2 was 58 years)[2] rather than females of reproductive potential, DPMH determined a lactation study will not be required at this time.

[22] Ballard O, et al. Human Milk Composition: Nutrients and Bioactive Factors. Pediatr Clin North Am. 2013 Feb; 60(1):49-74.

Females and Males of Reproduction Potential
DPMH recommends subsection 8.3 of labeling be omitted. There are no available data to suggest the components of Sutab adversely affect fertility. Pregnancy and contraception subheadings are not indicated because there are no available data to suggest the components of Sutab are associated with embryo-fetal toxicity.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. The recommendations below reflect input from the Clinical Pharmacology and Nonclinical Review Teams. DPMH discussed our labeling recommendations with the Division at the November 14, 2019 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Sutab Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Sutab use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Sutab.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation
Risk Summary
There are no available data on the presence of Sutab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sutab and any potential adverse effects on the breastfed infant from Sutab or from the underlying maternal condition.

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/s/

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11/15/2019 01:35:00 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 8, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213135
Product Name and Strength:	Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, 1.479 g, 0.225 g, and 0.188 g per tablet
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Braintree Laboratories, Inc
FDA Received Date:	May 15, 2019 and September 6, 2019
OSE RCM #:	2019-1052
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Sutab (sodium sulfate, magnesium sulfate, and potassium chloride) tablets, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Sutab prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Braintree submitted a 505(b)(2) NDA for Sutab (sodium sulfate, magnesium sulfate, and potassium chloride). We reviewed the prescribing information, carton labeling, and container label. We identified areas in the Sutab container label and carton labeling that can be improved to increase readability and prominence of important information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendation in Section 4.1 for the Applicant.

4.1 RECOMMENDATIONS FOR BRAINTREE LABORATORIES, INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-

readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. Lot number is required on all container and carton labels per 21 CFR 201.10(i); include the lot number on the label and ensure it is clearly differentiated from the expiration date.
3. To ensure consistency with the Prescribing Information, add the statement, "Recommended Dosage: See prescribing information."
4. Strength statement is missing. Add the strength statement below the established name.
5. Revise the "Preparation Procedure" to be consistent with the prescribing information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sutab received on September 6, 2019 from Braintree Laboratories, Inc.

Table 2. Relevant Product Information for Sutab	
Initial Approval Date	N/A
Active Ingredient	sodium sulfate, magnesium sulfate, and potassium chloride
Indication	an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.
Route of Administration	Oral
Dosage Form	tablets
Strength	1.479 g, 0.225 g, and 0.188 g per tablet
Dose and Frequency	Dose 1 – On the day prior to colonoscopy: • A low residue breakfast may be consumed, or only clear liquids on the day before colonoscopy. Examples of low residue foods are eggs, non-wheat baked goods (white bread), yogurt, grits, coffee, tea. • Early in the evening prior to colonoscopy, open one bottle of 12 tablets. • Fill the provided container with 16 ounces of water (up to the fill line). Swallow each tablet with a sip of water and drink the entire amount over 15 to 20 minutes. • Approximately one hour after the last tablet is ingested, fill the provided container a second time with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • Approximately 30 minutes after finishing the second container of water, fill the provided container again with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • If patients experience preparation-related symptoms (e.g. nausea, bloating, cramping), pause or slow the rate of drinking the additional water until symptoms diminish. Dose 2 -day of colonoscopy: • Continue to consume only clear liquids until after the colonoscopy. The morning of colonoscopy (5 to 8 hours prior to the colonoscopy), open the second bottle of 12 tablets.

	• Fill the provided container with 16 ounces of water (up to the fill line). Swallow each tablet with a sip of water and drink the entire amount over 15 to 20 minutes. • Approximately one hour after the last tablet is ingested, fill the provided container a second time with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • Approximately 30 minutes after finishing the second container of water, fill the provided container again with 16 ounces of water (up to the fill line) and drink the entire amount over 30 minutes. • If patients experience preparation-related symptoms (e.g. nausea, bloating, cramping), pause or slow the rate of drinking the additional water until symptoms diminish. • Complete all SUTAB tablets and water at least two hours prior to colonoscopy.
How Supplied	SUTAB (NDC 52268-201-01) is supplied as two bottles containing 12 tablets each. One container with a 16-ounce fill line.
Storage	Store at 20º to 25°C (68º to 77°F). Excursions permitted between 15º to 30°C (59º to 86°F). See USP controlled room temperature.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Sutab labels and labeling submitted by Braintree Laboratories, Inc.

- Container label received on May 15, 2019
- Carton labeling received on May 15, 2019
- Prescribing Information (Image not shown) received on September 6, 2019

B.2 Label and Labeling Images

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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