CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022372Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Date:	July 14, 2010
To:	Donna Griebel, MD, Director **Division of Gastroenterology Products (DGP)**
Through:	Claudia Karwoski, PharmD, Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)** Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide) Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution
Application Type/Number:	NDA 22-372
Applicant/sponsor:	Braintree Laboratories Inc.
OSE RCM #:	2010-1213

1. INTRODUCTION

This memorandum is in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the proposed Medication Guide (MG), proposed Risk Evaluation and Mitigation Strategy (REMS), and REMS supporting document for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution.

2. BACKGROUND

The application for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution, received July 2, 2008 had an original PDUFA goal date of May 2, 2009. The date was extended to August 2, 2009 based on a major amendment. Controversy concerning the adequacy of the safety evaluation led to the Division of Gastroenterology Products (DGP) taking the application to a CDER Regulatory Briefing on August 28, 2009. Subsequently, substantial postmarketing requirements had to be negotiated which delayed earlier action on the application.

The Medication Guide and REMS were determined by DGP and DRISK to be necessary for all bowel preparation products including SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution to ensure that the benefits of the drug outweigh the risks of fluid and electrolyte disturbances that can lead to serious adverse advents, including cardiac arrhythmias, seizures and renal impairment.

DRISK met with the DGP on June 14, 2010 to discuss changes to the Prescribing Information (PI) Warnings and Precautions section. DGP was provided with a draft DRISK review of the Medication Guide on June 17, 2010. On June 24, 2010 DRISK met with DGP to discuss the draft MG review. Changes to the Medication Guide based on discussion at the June 24, 2010 meeting are reflected in the attached Medication Guide review.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant. The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

3. MATERIAL REVIEWED

- Draft SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Prescribing Information (PI) received July 2, 2008, revised by the Review Division throughout the current review cycle, and received by DRISK on June 7, 2010.
- Draft SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Medication Guide (MG) received on July 2, 2008, and received by DRISK on June 7, 2010.

- SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated June 22, 2010
- Proposed SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on June 22, 2010

4. RESULTS OF REVIEW

In our review of the Medication Guide, we have:

- Simplified wording and clarified concepts where possible
- Ensured that the MG is consistent with the PI
- Removed unnecessary or redundant information
- Ensured that the MG meets the Regulations as specified in 21 CFR 208.24
- Ensured that the MG meets the criteria as specified in FDA's Guidance Useful Written Consumer Medication Information (published July 2006)

In our review of the proposed REMS and REMS Supporting Document, we have:

- Ensured it includes the elements outlined in the REMS Notification Letter
- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Division of Gastroenterology Products (DGP) and Applicant with regard to the MG and the proposed REMS.

Comments to the Division of Gastroenterology Products (DGP):

Our annotated MG is appended to this memo (Appendix A Marked Copy, Appendix B Clean Copy). Any additional revisions to the PI should be reflected in the MG.

Comments to Braintree Laboratories Inc.:

See the appended SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

a. **GOAL**

Revise your goal as follows:

The goal of this REMS for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution is to communicate the risks of serious fluid and serum chemistry abnormalities associated with osmotic bowel preparations to patients.

b. Under 21 CFR 208.24 (b), you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that an authorized dispenser can provide one Medication Guide with each new or refilled prescription. You state that each individual SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) will contain a Medication Guide which will be part of the (b) (4). We find your unit-of-use distribution plan acceptable.

c. Your plan to include a prominent statement on the SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) carton or container label that the Medication Guide enclosed in the kit should be dispensed to each patient is acceptable.

d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

We have some editorial comments in this section of the proposed REMS.

e. Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate). This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." If the plan is to conduct the required assessment using a survey, the submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate).

The submitted methodology lacks sufficient detail to complete a review.

1. Recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.

   Explain how often non-respondent follow-up or reminders will be completed.

   Explain how an incentive or honorarium will be offered, and the intended amount.

   Explain how recruitment sites will be selected.

   Submit for review any recruitment advertisements.

2. Define the sample size and confidence intervals associated with that sample size.

3. Define the expected number of patients to be surveyed to obtain the final proposed sample size, and how the sample will be determined (selection criteria)

4. The patient sample should be demographically representative of the patients who use SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate).

   If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.

5. Explain the inclusion criteria; that is, who is an eligible respondent. For example, *patient* respondents might be:
   - Age 18 or older
   - Currently taking SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) or have taken in past 3 months
   - Not currently participating in a clinical trial involving SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate)
   - Not a healthcare provider

   Submit any screener instruments, and describe if any quotas of sub-populations will be used.

6. Explain how surveys will be administered, and the intended frequency.

   Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person.

   Explain how surveyors will be trained.

7. Explain controls used to compensate for the limitations or bias associated with the methodology.

8. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.

   Potential respondents should be told that their answers will not affect their ability to receive or take SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate), and that their answers and personal information will be kept confidential and anonymous.

9. Respondents should not be eligible for more than one wave of the survey.

10. The assessment is to evaluate the effectiveness of the REMS in achieving the REMS goal by evaluating patients' knowledge of the serious risks associated with use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate). The assessment is not to evaluate consumer comprehension of the Medication Guide.

    Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an

opportunity to read or see the Medication Guide again prior to taking the survey.

11. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

12. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.

    Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate)?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs.

    The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.

    The order of the multiple choice responses should be randomized on each survey.

13. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.

    Respondents should not have the opportunity or ability to go back to previous questions in the survey.

    Explain if and when any education will be offered for incorrect responses.

14. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

15. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate). The Medication Guide is a paper handout that contains important information about the risks associated with use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) and how to use SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) safely. Medication Guides always include the title "Medication Guide" followed by the word SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about SUPREP Bowel Prep Kit

(sodium sulfate, potassium sulfate, and magnesium sulfate)," "What is SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate)," and "Who should not take SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate)."

16. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate)? (Select all that apply)
    a) My doctor or someone in my doctor's office
    b) My pharmacist or someone at the pharmacy
    c) Someone else - please explain: _____
    d) I did not get a Medication Guide for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate)

- Did you read the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

- Did you understand what you read in the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

- Did someone offer to explain to you the information in the Medication Guide?
    - Yes, my doctor or someone in my doctor's office
    - Yes, my pharmacist or someone at the pharmacy
    - Yes, someone else – please explain:
      _____
    - No

- Did you accept the offer? Yes or No

- Did you understand the explanation that was given to you?
    - All,
    - Most,
    - Some,
    - None

- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

17. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size,

mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

18. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

Please let us know if you have any questions.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22372	ORIG-1	BRAINTREE LABORATORIES INC	SUPREP BOWEL PREP KIT

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/s/

MELISSA I HULETT
07/14/2010

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07/15/2010
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Gastroenterology Products

NDA/BLA #s:	022372
Products:	SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) Oral Solution
APPLICANT:	Braintree Laboratories, Inc.
FROM:	Donna Griebel, M.D.
DATE:	June 22, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) to ensure that the benefits of the drug outweigh the risks of fluid and electrolyte disturbances that can lead to serious adverse events, including cardiac arrhythmias, seizures and renal impairment. In reaching this determination, we considered the following:

A. An estimate of the size of the population likely to use SUPREP Bowel Prep Kit is difficult and is influenced by the number of colonoscopies performed and the fact that alternative preparations are available for bowel cleansing in the US. Between 4 and 15 million Americans have the potential to be exposed to SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4), based on estimates in the literature of annual screening and diagnostic colonoscopy rates in the US in 2000.[i,ii]

B. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) is used as part of a bowel cleansing regimen to prepare the patient for colonoscopy. Screening colonoscopy is a procedure recommended by the

American Cancer Society[iii]. Screening colonoscopy can lead to early detection of colon cancer and adenomatous colon polyps, which if not removed could lead to colon cancer.

C. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) has been shown to be effective in cleansing the colon prior to colonoscopy. A poor preparation can lead to missed lesions. The current recommendation for colonoscopy for individuals of average risk for colon cancer begins at age 50 with follow-up every 10 years thereafter if the procedure does not detect lesions. The potential benefits of these products are adequate preparation prior to a colonoscopy permitting better visualization of polyps or cancers in the colon. Early detection of colon cancer can result in more effective treatment and survival advantage. Detection and removal of adenomatous polyps can interrupt their progression to cancer.

D. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) is administered for one course prior to colonoscopy. The whole course, including liquid intake and bowel cleansing, is finished within 24 hours.

E. Osmotic bowel preps can cause fluid and electrolyte disturbances. There have been reports of serious adverse events including cardiac arrhythmias, seizures and renal impairment associated with osmotic bowel preps. Risk factors for adverse events associated with fluid and electrolyte disturbances include hypovolemia, baseline kidney disease, and use of medicines that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]).

F. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4). FDA has determined that SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4). FDA has determined that SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) (b) (4) is a product for which patient labeling could help prevent serious adverse effects.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

[i] Brown ML, Klabunde CN, Mysliwiec P. Current capacity for endoscopic colorectal cancer screening in the United States: data from the National Cancer Institute Survey of Colorectal Cancer Screening Practices. *Am J Med* 115(2):129-133; 2003.
[ii] Laura C. Seeff, Thomas B. Richards, Jean A. Shapiro, et al. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastro* 127: 1670-1677; 2004.
[iii] Levin B, Lieberman DA, McFarland, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Published online March 5, 2008. *CA Cancer J Clin*. 2008; 58.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22372	ORIG-1	BRAINTREE LABORATORIES INC	SUPREP BOWEL PREP KIT

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/s/

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