

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022372Orig1s000

OTHER REVIEW(S)

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

Required by PREA

5. What type of study or clinical trial is required or agreed upon (describe)?

A data review to determine number of colonoscopies being performed in various pediatric age groups. The need to develop an age-appropriate formulation will be based on the colonoscopy utilization data obtained in this study.
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Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
PREA PMR

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: An Open-label Pilot Study Assessing the Efficacy and Tolerability of Suprep in ^{(b) (4)} Patients

PMR/PMC Schedule Milestones: Protocol Submission Date: 11/30/2013
Study Completion Date: 08/31/2014
Final Study Report Submission Date: 11/30/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Pediatric deferral granted at PeRC on 4-29-09 because adult studies are ready for approval.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

The drug has not been studied in the pediatric population.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

NA

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

An open-label pilot study assessing the efficacy and tolerability of SuPrep in in adolescents (12 to 16 years). The adult formulation (and any age appropriate reformulations) will be evaluated for tolerability and efficacy in this pilot study.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
Assesses tolerability

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
(provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
PREA PMR

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

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CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A Randomized, Single-blind, Multicenter Dose-ranging Study Comparing the Safety and Efficacy of SuPrep (3 doses) versus NuLYTELY in Adolescents (12 – 16 years of age).

PMR/PMC Schedule Milestones: Protocol Submission Date: 02/28/2015
Study Completion Date: 02/29/2016
Final Study Report Submission Date: 05/31/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Pediatric deferral granted at PeRC on 4-29-09 because adult studies are ready for approval.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

The drug has not been studied in the pediatric population.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

NA

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A Randomized, Single-blind, Multicenter Dose-ranging Study Comparing the Safety and Efficacy of SuPrep (3 doses) versus NuLYTELY in Adolescents (12 – 16 years of age).

Required

- Pharmacoepidemiologic study (list risk to be evaluated)
-
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
-
- Subpopulation (list type)
Pediatric patients 12-16 years
-
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
PREA PRM
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
-
- Other
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
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Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A Randomized, Single-blind, Multicenter Dose-ranging Study Comparing the Safety and Efficacy of SuPrep (3 doses) versus NuLYTELY in Children (3 – 11 years of age).

PMR/PMC Schedule Milestones: Protocol Submission Date: 08/31/2016
Study Completion Date: 08/31/2017
Final Study Report Submission Date: 11/30/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Pediatric deferral granted at PeRC on 4-29-09 because adult studies are ready for approval.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
 Animal efficacy confirmatory studies
 Pediatric requirement
 FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

The drug has not been studied in the pediatric population.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

NA

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A Randomized, Single-blind, Multicenter Dose-ranging Study Comparing the Safety and Efficacy of SuPrep (3 doses) versus NuLYTELY in Children (3 – 11 years of age).

Required

- Pharmacoepidemiologic study (list risk to be evaluated)
-
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
-
- Subpopulation (list type)
Pediatric patients 3-11 years
-
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
PREA PMR
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
-
- Other
-

6. Is the PMR/PMC clear and feasible?

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Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A Randomized, Single-blind, Multicenter Dose-ranging Study Comparing the Safety and Efficacy of SUPREP (3 doses) versus NuLYTELY in Infants and Children (Birth – 2 years of age).

PMR/PMC Schedule Milestones: Protocol Submission Date: 02/28/2018
Study Completion Date: 02/28/2019
Final Study Report Submission Date: 05/31/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Pediatric deferral granted at PeRC on 4-29-09 because adult studies are ready for approval.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

The drug has not been studied in the pediatric population.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

NA

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A Randomized, Single-blind, Multicenter Dose-ranging Study Comparing the Safety and Efficacy of Suprep (3 doses) versus NuLYTELY in Infants and Children (Birth – 2 years of age).
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Required

- Pharmacoepidemiologic study (list risk to be evaluated)
-
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
-
- Subpopulation (list type)
Pediatric patients birth - 2 years
-
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
PREA PMR
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
-
- Other
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A prospective, descriptive epidemiologic study to identify adverse events associated with SUPREP administration.

PMR/PMC Schedule Milestones: Protocol Submission Date: November 30, 2010
Study Completion Date: May 31, 2016
Final Study Report Submission Date: November 30, 2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

It is important to further evaluate the serious risks of fluid and electrolyte disturbances that can lead to serious adverse events including cardiac arrhythmias, seizures and renal impairment. In addition it is important to evaluate the serious risk of ischemic colitis.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

Available data from this NDA and for other drugs in the same pharmacological class indicate a serious risk of unexpected serious adverse events including fluid and electrolyte disturbances, in addition to ischemic colitis.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Serious adverse events including cardiac arrhythmias, seizures and renal impairment.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A prospective, descriptive epidemiologic study to identify adverse events associated with SUPREP administration in 20,000 patients undergoing screening colonoscopy and 20,000 patients in an appropriate control group. This study should be conducted in a data resource with access to electronic medical records (EMR); a claims-only database is insufficient. The eligible population will be all patients prescribed SUPREP. Outcomes of interest are those that occur within three months of SUPREP administration.

- a. Include demographics (age, ethnicity, gender).
- b. Information to collect: lab results, concomitant medications, and co-morbidities, to be collected at baseline (pre-colonoscopy) and at time of adverse event, together with any intervening data.
- c. Outcomes of interest: all deaths; all serious adverse events; new or worsening diagnoses of ischemic colitis, renal insufficiency/failure or other renal conditions, seizure disorders, heart disease, or gout; new diagnoses of arrhythmia; and emergency department visits.
- d. Results are to include counts, frequencies, and incidence rates by baseline renal function, pre-existing heart disease, concomitant drug use, and any other relevant parameters, including age, gender, etc.
- e. Additional analyses are to include correlation of adverse events with population subgroups.
- f. Interim reports are to be submitted annually. Crude exposure and event counts are to be submitted every six months.

Required

- Pharmacoeconomic study (list risk to be evaluated)
see above

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
(provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
 - Dose-response study performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A randomized, active control, single-blind trial to evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUPREP Bowel Prep Kit prior to colonoscopy.

PMR/PMC Schedule Milestones: Protocol Submission Date: November 30, 2010
Study Completion Date: November 30, 2012
Final Study Report Submission Date: May 31, 2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

It is important to further evaluate the serious risks of fluid and electrolyte disturbances that can lead to serious adverse events including cardiac arrhythmias and renal impairment.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

Available data for other drugs in the same pharmacological class indicate a serious risk of unexpected serious adverse events including fluid and electrolyte disturbances.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Serious adverse events including cardiac arrhythmias, seizures and renal impairment.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A randomized, active control, single-blind trial to evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUPREP Bowel Prep Kit prior to colonoscopy.

a. The study population should include the general population and a substantial proportion of renal impairment and elderly patients.

b. Each dosage regimen approved needs to be tested. For each dosage regimen, the total number of patients enrolled should be similar to the total number of patients enrolled in that dosage regimen in the prior pivotal studies.

c. The study will need to capture timing of dosing, and timing of pre-colonoscopy safety and laboratory assessments.

d. Safety assessments should include orthostatic heart rate and blood pressure, ECGs, and symptom assessment with detailed narratives. These safety assessments should be done at baseline and pre-colonoscopy. Symptom assessments should also be done three days post-colonoscopy, and seven days post-colonoscopy.

e. Laboratory assessments should include CKs (abnormal CKs should be fractionated), serum chemistry, urinalysis with microscopic analysis, urine electrolytes, and sulfate. These assessments should be conducted at baseline, pre-colonoscopy (at the same time as the pre-colonoscopy ECG), three days post-colonoscopy, and seven days post-colonoscopy.

f. Colonoscopy observations of the presence and extent of aphthous ulcerations and other findings indicative of ischemic colitis should be recorded systematically.

g. New abnormalities should be followed until resolved or stable.

h. Long-term follow-up at one month post-colonoscopy, three months post-colonoscopy, and six months post-colonoscopy should include serum chemistry, medication history, urinalysis with microscopic analysis, and adverse event history.

i. Please explore the use of biomarkers for tubular and glomerular injury such as KIM 1 and Cystatin C and consider retaining patient samples for future testing for biomarkers.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
renal and metabolic toxicity and sulfate levels

- Subpopulation (list type)
includes elderly, renal impairment and hepatic impairment

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
(provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
 - Dose-response study performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other _____
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking SUPREP Bowel Prep Kit.

PMR/PMC Schedule Milestones: Protocol Submission Date: November 30, 2010
Study Completion Date: February 29, 2012
Final Study Report Submission Date: August 31, 2012

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

It is important to further evaluate the serious risks of fluid and electrolyte disturbances that can lead to serious adverse events including cardiac arrhythmias.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

Available data for other drugs in the same pharmacological class indicate a serious risk of unexpected serious adverse events including fluid and electrolyte disturbances.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Serious adverse events including cardiac arrhythmias.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking SUPREP Bowel Prep Kit.

- a. The study population should include a substantial number of healthy, renal impairment, hepatic impairment, and elderly patients (at least 12 per group).
- b. Assessments should include ECG performed between five and eight hours after completion of dosing.
- c. Lab assessments should consist of serum chemistry, including calcium and magnesium, at the same time as the ECG.
- d. Study will need to capture timing of dosing, and safety and laboratory assessments.
- e. This study might be incorporated as a substudy of Study 1.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
cardiac arrhythmias

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
(provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
ECG study

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22372

ORIG-1

BRAINTREE
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INC

SUPREP BOWEL PREP KIT

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/s/

MATTHEW C SCHERER
08/03/2010

JOYCE A KORVICK
08/03/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: June 9, 2010

To: Matthew Scherer, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Shefali Doshi, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Robert Dean, DTC Group Leader
Kathleen Klemm, Regulatory Review Officer
Wayne Amchin, Regulatory Project Manager
DDMAC

Subject: NDA 022372

DDMAC labeling comments for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution

In response to DGP's May 28, 2010 consult request, DDMAC has reviewed the draft Medication Guide for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution that was sent electronically by DGP on June 6, 2010.

The PI used as the basis for DDMAC's comments on the draft Medication Guide is titled "SuPrep PI- for revision.doc" which was last modified in the eroom on March 11, 2010 at 12:37 pm.

DDMAC's comments on the draft Medication Guide are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the Medication Guide, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

4 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/

SHEFALI S DOSHI

06/09/2010

Division of Cardiovascular and Renal Products

Consult: From the Division of Gastroenterology Products

NDA: 22372

Sponsor: Braintree Laboratories

Drug: SuPrep/ BLI800

Indication: Bowel Cleansing for Colonoscopic Procedures

Consulting Medical Officer: Melanie Blank, MD

Date of Consult: 09/03/09

Date of Completion: 10/08/09

Questions for Consultant:

DGP requests your assistance in our efforts to develop a required safety study as either required for approval or a PMR for NDA 22-372 (SuPrep Bowel Prep Kit). SuPrep is a sulfate-based bowel cleanser. We are considering requiring an additional single-dose study that would involve a screening/baseline visit, with a single exposure to SuPrep, and laboratory testing at various times afterwards.

DGP has the following specific questions:

1. What sort of monitoring, including specific evaluations, frequency and duration, would be required to detect a renal injury signal?

Answer: The most efficient way to detect a renal injury signal in a new clinical trial with BLI800 would be to study the drug in patients who have baseline renal insufficiency. Patients with CrCl > 60 cc/min have considerable renal reserve. Even in the presence of substantial nephron injury, no changes in serum creatinine might be observed in patients with adequate renal reserve. A kidney with substantial renal reserve can, despite extensive injury, retain function through hyperfiltration or through the recruitment of underutilized nephrons. To study the risk of renal injury, patients with mild to moderate (stage 3) renal disease (CrCl \geq 30 ml/min and < 60 mL/min) and stage 4 renal disease (CrCl \geq 15 ml/min and < 30 mL/min) should be enrolled. These patients have less or no renal reserve and would be expected to have increases in serum creatinine with even minor renal injury. In addition to testing serum creatinine, it would also be worthwhile to test the patients' serum for BUN and the patients' urine for albumin, other standard markers of renal injury. Other novel biomarkers that might be more sensitive for detecting renal tubular injury in the clinical setting are urinary Cystatin C, and KIM 1. If the sponsor is interested in assessing changes in these novel biomarkers of kidney injury, they may contact Elizabeth Gribble Walker, PhD, Director, Predictive Safety Testing Consortium, Critical Path Institute, 1730 E River Rd, Ste 200, Tucson, AZ 85718, 520.647.8375, ewalker@c-path.org for more information.

Creatinine, BUN, urinary albumin and other renal biomarkers should be measured at baseline, at day -1, at pre-colonoscopy, at 72 hours post-colonoscopy, at 1 week post-colonoscopy, and at 1 month post-colonoscopy.

2. Please recommend an intervention for patients who have documented elevations in creatinine after treatment.

Answer: If a patient develops an elevation in serum creatinine, the patient should be managed appropriately, considering the degree of elevation. The patient should be worked up for other causes of renal dysfunction if there is a substantial change in renal function, i.e., doubling of serum creatinine. Because of the volume depletion that is expected to result from the study, volume resuscitation should be provided. All medications that can interfere with volume status and renal hemodynamics or contribute to renal injury, such as diuretics, NSAIDs, ACEs and ARBs should be discontinued if possible. Monitoring of kidney function should be done frequently (daily or every two days for the first week, weekly for the first month, and then biweekly or monthly) and the patient should be followed clinically until resolution of the kidney injury and/or for 6 months.

3. Please comment on the known renal effects of sulfate and if any specific adverse effects (including electrolyte abnormalities) should be expected based on known mechanisms. For example, some patients in the SuPrep studies had elevated uric acid.

Answer: Sulfate is known to cause diarrhea, metabolic acidosis and worsening of ulcerative colitis. There are no known direct effects of sulfate on the kidney. However, sulfate-induced metabolic acidosis will cause decreased reabsorption of calcium and magnesium. Acidosis will also tend to decrease uric acid excretion.

Elevated uric acid levels were seen in the BLI800 treatment groups of the two studies. Hypocalcemia was seen in the patients that were studied in the PK study reviewed by Dr. Bai.

The rise in serum uric acid in the BLI800 treated patients probably resulted from excess volume depletion, although one cannot be sure that this is the etiology. The BLI800 treated patients had increased vomiting and also had a higher percentage of “excellent preparations” than the patients in the MoviPrep group. Volume depletion leads to hyperuricemia. Three other possibilities for the etiology of increased uric acid serum levels with BLI800 are 1) interference with renal tubular secretion of uric acid, 2) decreased urine pH, and 2) increased uric acid production. It would be interesting to monitor the patients for fractional excretion of uric acid (FE-UA), urine uric acid/ urine creatinine. In the setting of hyperuricemia, one would expect an increase in FE-UA, unless there is interference with excretion or secretion. In the safety study that is being planned, it will be useful to measure the fractional excretion of uric acid (FE-UA) and the urine pH. Usually, elevated urine pH will cause increased uric acid excretion and decreased serum uric acid levels.

If the uric acid formation is increased, one would expect a high FE-UA. If the uric acid excretion/secretion is decreased, one would expect a low FE-UA.

There is evidence that sulfate can cause complexation with calcium. It may interfere with reabsorption of calcium and magnesium. Monitoring calcium and magnesium levels should be done again in future trials and ECGs at Cmax should be done as well. Another PK study where

serum pH, urine pH, anion gap, serum calcium, serum magnesium and serum and urine uric acid is measured at several intervals post-ingestion would be useful for understanding the metabolic effects of BLI800.

Other Comments (See review below for further analysis and justification):

1. Metabolic acidosis is associated with sulfate ingestion. For this reason, patients with more severe kidney disease should be studied to ensure that BLI800 does not cause worsening of their metabolic acidosis. They should also be studied to check its effect on uric acid, calcium and magnesium levels in this patient population.
 2. While there were no cases of gout in the pivotal trials, it may be advisable to have a word of caution in the label for patients who have a history of gout because of the large increases in serum uric acid concentrations in some patients.
 3. Sulfate and undigested sulfur compounds have been implicated in the etiology of ulcerative colitis. The proposed label states that BLI800 should be used with caution in patients with ulcerative colitis. It may be best to not use this product in patients with ulcerative colitis unless there is further study.
-

MY REVIEW

Review Strategy:

NDA 22372 was submitted on 7/1/08 and a major amendment was submitted on 8/7/09. A regulatory decision has not yet been reached. The sources I used for my review are Dr. Jasmine Gatti, MD's clinical review, Dr. Tamal K. Chakraborti, Ph.D's Toxicology Review, and Dr. Peifan J. Bai's Clinical Pharmacology Review. I also did some of my own analyses and literature searches.

General Study Design and Primary Efficacy Result:

Braintree Laboratories conducted two phase 3 trials to support their application for SuPrep (BLI800) for colonic bowel preparation before colonoscopy. The 2 pivotal studies, under IND 74808, involved 2 randomized 1:1, parallel, multi-center, single-blind Phase 3 studies of BLI800 vs. MoviPrep® in 400 adults using a same day split dose (Study 301) and in 400 adults using a two day split dose (Study 302). Aside from the dosage regimen, the studies were identical. Patients had baseline laboratory tests on Day -1, then took the assigned medication and returned for colonoscopy Visit 2 where AEs and more laboratory tests were gathered. A couple of weeks later the patients had a follow-up visit. The studies met their primary endpoints for noninferiority of SuPrep (BLI800) as a bowel preparation for colonoscopy as compared to MoviPrep, as assessed by the investigators for quality of preparation. Both agents were more effective when taken over two days.

Chemical and Pharmacodynamic Descriptions of Drug (SuPrep/BLI800) and Active Comparator (MoviPrep):

SuPrep (BLI800) is an oral sulfate solution and is given in a split dose with each dose followed by 32 oz. of water. It is composed of the following active ingredients: sodium sulfate (35 g), potassium sulfate (6.3 gm), magnesium sulfate (3.2 g). MoviPrep is a marketed formulation of the following active ingredients: ascorbic acid (9.4 gm), polyethylene glycol 3350 (200 gm), potassium chloride (2.03 gm), sodium ascorbate (11.8 g), sodium chloride (5.38 gm) and sodium sulfate (15 gm). When reconstituted it is a 2 L formulation. It is a Salix product for bowel cleansing that was approved in 8/2/06. The pharmacodynamic action of these preparations relies on the retention of water in the intestines. In SuPrep the primary osmotically active agents are magnesium and sulfate, with sulfate contributing the larger proportion of osmotic load. Both are poorly absorbed above a point of saturation, forcing water to remain in the intestines. In MoviPrep, the osmotically active agents are polyethylene glycol and sodium sulfate, but at less than half the dose that is in SuPrep.

Preclinical Safety:

According to the preclinical review done by Dr. Chakraborti, the systemic toxicity of Suprep/BLI800 was adequately tested in rats and dogs. SuPrep was administered orally (gavage) to rats and dogs for up to 28 days up to a maximum daily dose of 5 g/kg/day (approximately 0.9 and 3 times, respectively, the recommended human dose of 44.48 g/day or 0.89 g/kg based on the body surface area). SuPrep caused diarrhea, electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis. In dogs, SuPrep caused emesis, excessive salivation, excessive drinking of water and abnormal excreta (soft and/or mucoid feces and/or diarrhea), increased urine pH and sodium excretion.

Clinical Safety:

The clinical safety profile of SuPrep was overall very good except for a high rate of nausea and vomiting.

Deaths: There was only one death in a MoviPrep patient who had respiratory arrest. The respiratory arrest was a complication of a laparoscopic colonic resection that occurred over 1 month after he took the study drug.

Serious Adverse Events: There were 2 serious adverse events in patients that took MoviPrep. One was a patient with atypical chest pain that occurred 14 days after the last dose of MoviPrep. The other was a patient with a colonic perforation that occurred as a complication of the colonoscopy. The patient had taken MoviPrep on the day before and the day of colonoscopy.

Dropouts: The dropout rate for the two studies combined was 7% according to Dr. Gatti's review, including screening failures. None of the screening failures took SuPrep or MoviPrep. There were only 4 dropouts out of 787 patients due to adverse events. One patient on SuPrep developed AV block and was discontinued from the study. 3 of the other patients that dropped out due to adverse events had nausea, vomiting or bloating. 3 or the 4 patients that dropped out because of adverse events had taken BLI800.

Common Adverse Events (AEs): The most common AEs were abdominal pain, abdominal distension, nausea, vomiting, headache and discomfort. The only notable

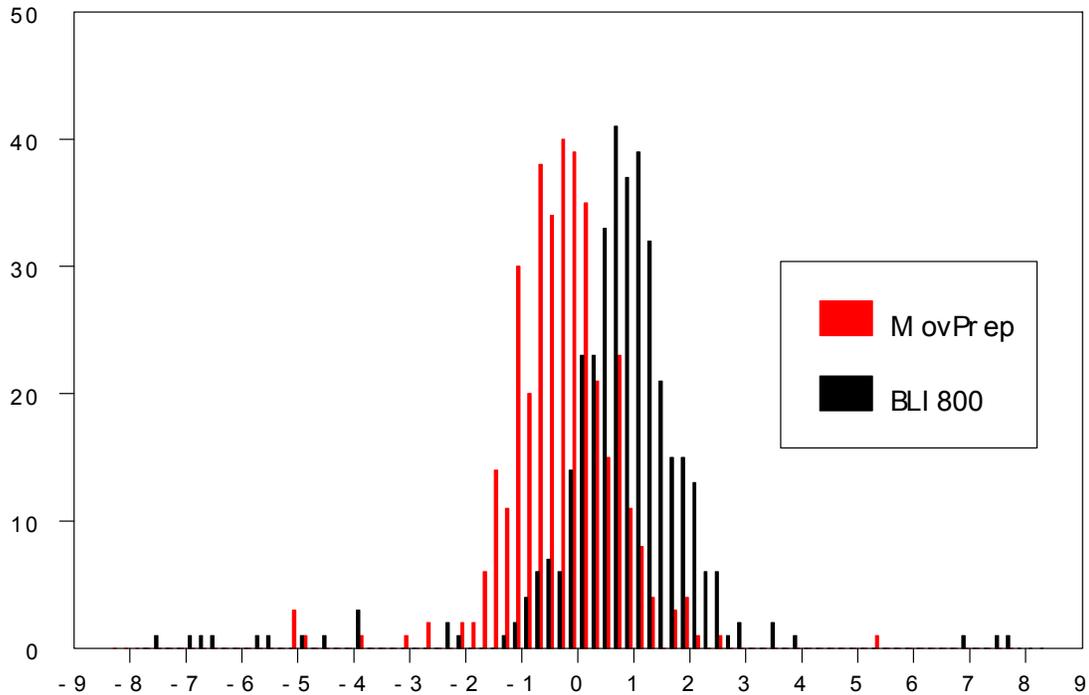
differences in these common AEs between the BLI800 and MoviPrep were nausea (40% vs. 35%) and vomiting (10% vs. 4%).

Laboratory:

BUN and Creatinine: In the NDA clinical review, the medical officer, Dr. Jasmine C. Gatti, provided a table (301-17 from NDA section 14) which demonstrated virtually no mean changes in serum creatinine from baseline (within 15 days prior to colonoscopy) to Visit 2 (day of colonoscopy) or Visit 3 (30 days post colonoscopy) for either BLI800 or MoviPrep. Mean baseline readings were approximately 1 mg/dL with a standard deviation of approximately 0.20 mg/dL. BUN mean baseline readings were approximately 16.5 mg/dL, decreased by approximately 3 mg/dL by Visit 2 and were close to baseline by Visit 3. These were no statistically significant differences between the two drugs for changes in BUN or Creatinine. The elevation of BUN at visit 2 was probably due to volume depletion.

Uric Acid: There was a mean rise in uric acid concentration of 0.59 (SD=0.8) mg/dL (in study 301) and 0.44 (0.84) mg/dL in study 302 between baseline and visit 2 in the BLI800 group with essentially no difference in the MoviPrep group in both studies. There was a strongly statistically significant difference between the treatment groups ($p < 0.001$). While there were no corrections for multiplicity, a p value < 0.001 is impressive and the difference was seen in both studies. It is clear from the histogram in Figure 1 that in general there is an increase in uric acid levels in the BLI800 group. There is also, however, a much greater variance in the BLI800 group in uric acid differences from baseline. While there are greater increases, there are also greater decreases.

Figure 1: Distribution in Change of Uric Acid Levels from Baseline to Visit 2 (Colonoscopy Visit) in combined studies 301 and 302



In the preclinical studies that were described in Dr. Chakraborti's review, animals treated with BLI800 had alkalinized urine. One might imagine that urine pH would be elevated in the clinic as well which would cause a uricosuric effect and a decrease in serum uric acid concentration. The observation that bicarbonate levels decreased in the treated patients suggests that the patients may have had a metabolic acidosis and the urine may, in fact, not have been alkaline. Another factor at work, however, might be the overall volume contraction in these patients which may have been greater in the BLI800 treated patients because of increased vomiting. Contraction of the extracellular fluid volume which causes a substantial decrease in uric acid clearance in rats and presumably in humans may have caused decreased excretion of uric acid in the BLI800 treated patients. (Weinman et al, *Jl of Clin Inv*, Vol 55, February 1975, 283-291. Another possibility is that sulfate could interfere with secretion of uric acid but there is no evidence in the literature to support this possibility.

It is not clear if the increase in uric acid is a consequence of increased uric acid formation or decreased uric acid excretion/ secretion. In the safety study that is being planned, it will be useful to measure the fractional excretion of uric acid (FE-UA) and the urine pH. The FE-UA is the ratio between uric acid and creatinine clearances. If the uric acid formation is increased, one would expect a high FE-UA. If the uric acid excretion/secretion is decreased, one would expect a low FE-UA.

While there were no cases of gout in the pivotal trials, it may be advisable to have a word of caution in the label for patients who have a history of gout because of the large increases in serum uric acid concentrations in some patients.

Serum Chloride and Serum Bicarbonate: There was a decrease in mean serum chloride concentration of -0.71 (SD=2.6) mEq/L in study 301 and -0.75 (3.1) mEq/L in the BLI800 group and an increase of 1.61 (SD=2.4) and 0.89 (2.8) mEq/L in the MoviPrep group respectively in the two studies. The serum bicarbonate levels were somewhat decreased in both studies with the decrease being statistically significantly greater in the MoviPrep group than in the BLI800 group in both studies. While these changes may not be of great clinical significance, metabolic acidosis has been shown to result from consumption of “flowers of sulfur,” a fine, yellow powder that is more than 99.5 percent pure sulfur (Blum and Coe, 1977 Blum JE, Coe FL. 1977. Metabolic acidosis after sulfur ingestion. N Engl J Med 297:869–870. For this reason, patients with more severe kidney disease should be studied to ensure that BLI800 does not cause a severe metabolic acidosis in these patients who are usually acidotic.

Sulfate: In the PK study, 202, it was noted by Dr. Bai that baseline levels of sulfate are higher in patients with mild to moderate renal insufficiency and that at Cmax, the levels are substantially higher in these patients.

In Table 1, constructed from data from Dr. Bai’s review, it can be seen that the serum sulfate concentration peaks at the same time in renal failure patients (who had a mean GFR of 44 (SD =2.65) mL/min/1.73 m²) and in normals (16 -17 hours) and that the corrected for baseline Cmax levels are approximately 717 µM/L and 500 µM/L, respectively.

The predose levels of sulfate were much higher in patients with renal impairment than in normal subjects (607 µM/L vs. 335 µM/L). Renal impairment resulted in 53.6% higher mean AUC and 43.5% higher mean Cmax than healthy subjects. However, it should be noted that the per cent increase of sulfate levels from baseline was actually higher in the normals (48%) than in the patients with renal insufficiency (18%).

Serum sulfate did decline to predose level by day 6 in both groups. Respective mean predose and day 6 serum sulfate levels were 335 µmol/L and 349.2 µmol/L in healthy subjects. By pre-noon on Day 3 and Day 6, mean (SD) serum sulfate concentrations were 617.8 µmol/L and 574.7 µmol/L in moderate renal disease patients, respectively, showing no statistical differences from the mean predose concentrations of 607.0 µmol/L.

Table 1: Sulfate pharmacokinetics in healthy patients and patients with mild to moderate renal insufficiency

	Healthy Subjects	Renal Insufficiency Patients with a mean GFR of 44 (SD =2.65) mL/min/1.73 m ²
	N=6	N=6
Baseline Sulfate	335.0 (34.44%)	607.0 (31.66%)

Levels ($\mu\text{mol/L}$) (SD)		
After SuPrep		
Cmax ($\mu\text{mol/L}$) (SD)	499.50 (33.03%)	717.0 (37.77%)
AUC(0-tau) ($\mu\text{mol}\cdot\text{hr/L}$) (SD)	8,029.88 (42.65%)	12,332.95 (34%)
Tmax (hr) (SD)	16.80 (48.47%)	17.5 (16.85%)
T1/2 (hr) (SD)	8.51 (53.76%)	10.16 (91.76%)
Approximate # of days before return to baseline	6	3-6

BACKGROUND ON SULFATE:

Sulfate is contained in many commonly ingested foods and is an important dietary requirement for making sulfate containing amino acids. Sulfate ingestion from drinking water is variable but some well water in rural areas of the U.S. has been known to contain upwards of 500 mg/L and some of the “mineral” waters sold with health claims have been reported to exceed this level.

The following material was taken from the Dietary Reference Intakes for Water, Potassium, sodium, Chloride and Sulfate, by the Panel on Dietary Reference Intakes for Electrolytes and Water, Institute of Medicine, published by the National Academies Press, Copyright 2005 by the National Academy of Sciences.

Known adverse effects of overconsumption of sulfate:

Metabolic Acidosis. Sulfate causes an increased anion gap metabolic acidosis. (Acid-Base Physiology, 3.2, http://www.anaesthesiamcq.com/AcidBaseBook/ab3_2.php). The metabolic acidosis also increases sulfate excretion (Pelis R et al, Amer JI of Phys. Renal physiology 205;289(1): F208-16.). Perhaps this explains why the patients with mild renal insufficiency had sulfate levels return to normal more rapidly than the normal patients. Metabolic acidosis may also cause increased urinary calcium and magnesium excretion.

Diarrhea. Osmotic diarrhea and loose stools have been reported with high intakes of sulfate consumed in water. (Backer, 2000, CRC Reviews in Clinical Laboratory Sciences, 37(4):389-400.). Magnesium sulfate is given intravenously in various clinical situations. Deemed to be safe and effective when used to prevent eclampsia during pregnancy, serum sulfate concentration was increased approximately twofold in 11 pregnant women treated with magnesium sulfate (Ricci et al, 1990). The sponsor also cited literature regarding pharmacokinetics of sulfate. Baseline sulfate levels also appear to be elevated in patients with preeclampsia. Morris and Levy (Morris ME and Levy G. Clin Pharmacol Ther. 1983; 33:529-36) reported that serum levels rose from a baseline of 410 μM to 510 μM two hours after an oral dose of 9.0 g of sodium sulfate. When

magnesium sulfate was given intravenously as a preventive for eclampsia, serum levels rose from 850 to 1550 μM (Ricci J et al., Am J Nephrol. 1990; 10:409-11).

Adverse reactions associated with magnesium sulfate in four trials were compiled in a review article on the topic of the use of magnesium sulfate prophylaxis in preeclampsia (B.Sibai, Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials American Journal of Obstetrics and Gynecology, Volume 190, Issue 6, Pages 1520-1526). The adverse reactions were feeling warm, flushed, nausea or vomiting, muscle weakness, dizziness and irritation at the site of injection. There are cases in the literature of maternal death because of hypermagnesemia in patients treated with magnesium sulfate. It is more likely that the deaths were a result of the hypermagnesemia (as opposed to hypersulfatemia) because the deaths were acute cardiac arrest, a known complication of hypermagnesemia.

Increased serum sulfate concentration results in increased complexation with calcium. (Cole and Evrovski, 2000 Cole DEC, Evrovski J. 2000. The clinical chemistry of inorganic sulfate. Crit Rev Clin Lab Sci 37:299–344.; Michalk et al.1981, Proc Eur Dial Transplant Assoc 18:561-566). Patients in the PK trial 202 had a slight decrease in serum calcium. While this is not likely to be clinically relevant in most clinical conditions, elevation of serum sulfate could worsen hypocalcemia. It may be beneficial to study this more carefully. In Dr. Bai's review, there was some concern raised about decreased serum calcium in the PK study 202. In 4 patients, the hypocalcemia was associated with bradycardia. In the pivotal trials there was no trend for mean decreases in serum calcium. The patient that dropped out because of AV block (10038) did not have a decrease in serum calcium level. The calcium level was 9.6 mg/dL at baseline and at colonoscopy. However, since there is this possibility of sulfate complexation with calcium, it is sensible to study serum calcium more closely in the planned follow-up safety study.

Ulcerative Colitis

Sulfate and undigested sulfur compounds have been implicated in the etiology of ulcerative colitis. Roediger et al, Colonic sulfide in pathogenesis and treatment of ulcerative colitis. Dig Dis Sci 42:1571–1579. 1997). Excess luminal sulfide is thought to overburden mucosal detoxification systems, resulting in impaired butyrate oxidation and colonic epithelial inflammation. The proposed label states that BLI800 should be used with caution in patients with ulcerative colitis. It may be best to not use this product in patients with ulcerative colitis unless there is further study.

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/

MELANIE J BLANK
10/13/2009

NORMAN L STOCKBRIDGE
10/14/2009



**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: August 7, 2009

To: Donna Griebel, MD, Division Director
Division of Gastroenterology Products (DGP)

Through: Jodi Duckhorn, MA, Team Leader
Division of Risk Management (DRISK)

From: Barbara Fuller, RN, MSN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Instructions for Use)

Drug Name(s): SuPrep Bowel Prep Kit

Application Type/Number: NDA 22-372

Applicant/sponsor: Braintree Laboratories, Inc

OSE RCM #: 2009-1202

1 INTRODUCTION

This review is written in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Instructions for Use (IFU) for SuPrep Bowel Prep Kit (Sodium sulfate, potassium sulfate, magnesium sulfate). Please let us know if DGP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft SuPrep Bowel Prep Kit (Sodium sulfate, potassium sulfate, magnesium sulfate) Prescribing Information (PI) submitted July 1, 2008 and revised by the Review Division throughout the current review cycle.
- Draft SuPrep Bowel Prep Kit (Sodium sulfate, potassium sulfate, magnesium sulfate) Instructions for Use (IFU) submitted on July 1, 2008.

3 RESULTS OF REVIEW

In our review of the IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information

Our annotated IFU is appended to this memo. Any additional revisions to the PI should be reflected in the IFU.

Please let us know if you have any questions.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

BARBARA A FULLER

08/07/2009

SuPrep DRISK Final Review

JODI M DUCKHORN

08/07/2009

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: April 14, 2009

To: Matthew Scherer, Regulatory Project Manager
Division of Gastroenterology Products

From: Shefali Doshi, Regulatory Review Officer
Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Robert Dean, Group Leader
Sangeeta Vaswani, Acting Group Leader
DDMAC

Subject: **NDA 22-372 SuPrep Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) solution concentrate for oral administration**

DDMAC labeling comments for SuPrep Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) solution concentrate for oral administration

DDMAC has reviewed the proposed product labeling (PI), bottle label, carton label, and [REDACTED] (b) (4) for SuPrep Bowel Prep Kit (SuPrep) submitted for consult to DDMAC on April 1, 2009.

DDMAC's comments on the proposed PI, bottle label, carton label, and [REDACTED] (b) (4) are based on the proposed product labeling (PI) from April 7, 2009.

Thank you for the opportunity to comment on this proposed label.

If you have any questions on the comments for the PI and bottle label, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

If you have any questions on the comments for the patient labeling [REDACTED] (b) (4) or container label, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

DDMAC offers the following comments on the proposed PI:

General Comments

Please apply our comments on the full PI to the Highlights section, where applicable.

As discussed during the April 6, 2009 labeling meeting, [REDACTED] (b) (4)

Full PI

Indications and Usage

This section states, “SuPrep Bowel Prep Kit is indicated for cleansing of the colon as preparation for colonoscopy in **adults**” (emphasis added). Please consider adding context for the bolded text (i.e., a specific age range, such as, “adults, 18 years of age or older”).

Dosage and Administration

This section states, [REDACTED] (b) (4)

[REDACTED] DDMAC suggests deletion of this text from this section.

Warnings and Precautions

DDMAC notes that the approved PI for MoviPrep includes additional information in this section. Specifically, the PI for MoviPrep states, “If a patient experiences severe bloating, abdominal distension, or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms abate.” [REDACTED] (b) (4)

[REDACTED] Should this additional context be included in the Warnings and Precautions section of the SuPrep full PI?

The Not for Direct Ingestion subsection [REDACTED] (b) (4)

[REDACTED], DDMAC suggests deletion.

Adverse Reactions

The Clinical Studies Experience subsection [REDACTED] (b) (4)

(b) (4)

DDMAC suggests deletion of the bolded text as it appears repetitive.

Drug Interactions

(b) (4)

Also, the text, “[T]he medication may not be absorbed properly” is vague. Please consider providing additional context for this text (e.g., do certain medications need to be held or dosed differently while the patient is taking SuPrep, etc.?)

Use in Specific Populations

The Pediatric Use subsection (8.4) states, “Safety and effectiveness in **pediatric patients** have not been established” (emphasis added). Please consider providing context for the bolded text (e.g., specific ages).

The Geriatric Use subsection (8.5) states,

(b) (4)

DDMAC suggests adding context if available (e.g., specific numbers/incidence rates of vomiting).

Clinical Pharmacology

(b) (4)

Is this text accurate and supported by substantial evidence? If not, DDMAC suggests deletion.

The Pharmacokinetics subsection (12.3) includes the text, “was similar between . . .” DDMAC is concerned that this text is vague. Please consider adding context for these statements (e.g., specific values for comparison, if available).

Clinical Studies

(b) (4)

Is this text essential? DDMAC suggests deleting this text and allowing the data to speak for itself.

How Supplied/Storage and Handling

Is the diluted solution allowed to be stored, or should it be consumed immediately? Should additional context regarding storage of the diluted solution be added to the Storage subsection?

Patient Counseling Information

This section should contain information that a prescriber should discuss with the patient (e.g., most important safety issues from the main safety sections of the label, and/or any important information on proper dosing, registries). We recommend revising this section to incorporate all of these important concepts, as appropriate.

DDMAC offers the following comments on the proposed bottle label

General Comments

The proposed bottle label states, “This bottle contains 6 ounces (177 mL) of liquid bowel prep.” Should additional context be added to convey that this solution must be further diluted prior to ingestion?

DDMAC offers the following comments on the proposed carton label:

General Comments

We note that MoviPrep has two ways in which the preparation may be taken and that both sets of instructions are on its carton label. (b) (4)

(b) (4)
the proposed carton label only provides instructions for “overnight” preparation. (b) (4)

Panel 5 of the proposed carton label is titled, “Instructions for Use” and provides instructions for what needs to be done the day before colonoscopy with regards to diet. Panel 2 of the proposed carton label provides instructions regarding what needs to be done the evening before and the day of colonoscopy. We are concerned that patients may not read the instructions on panel 5 prior to reading the instructions on panel 2.

Please apply the following comments to the specific panels.

Panel 1

(b) (4)

(b) (4)

We recommend revising this statement to be more specific as to exactly when the instructions should be read.

Panel 5

(b) (4)

The Dosage and Administration section of the proposed PI does not provide instructions about what can or cannot be eaten for lunch and dinner the day before colonoscopy. Is this accurate? We recommend that the Dosage and Administration section of the proposed PI and the instructions on panel 5 of the proposed carton label be consistent.

The proposed panel also includes a list of clear liquids that are okay to drink; however, these are not listed in the proposed PI. Is this list accurate?

Panel 2

We recommend that the proposed instructions be revised to convey that all of the steps should be performed using the mixing cup that is provided in the kit.

The Dosage and Administration section of the proposed PI states that on the day of colonoscopy, patients are only to have clear liquids until after the colonoscopy and that red and purple liquids, milk, and alcoholic beverages are to be avoided. We recommend including these instructions in the beginning of the proposed "Day of procedure" section.

We recommend including the instruction that the dose of SuPrep on the day of colonoscopy should be taken at least 10-12 hours after the evening dose of SuPrep.

(b) (4)

the Dosage and Administration section of the proposed PI, which states that patients should drink two additional containers filled to the 16 oz line with water over the next hour.

(b) (4)

This is inconsistent with the Dosage and Administration section of the proposed PI, which states that all study preparation and required water are to be completed at least one hour prior to colonoscopy.

[Redacted] (b) (4)

Should the reason why SuPrep should be properly diluted be conveyed to patients (because nausea, vomiting and dehydration may result if there is direct ingestion of the undiluted concentrate, as conveyed in the Warnings and Precautions section of the proposed PI)?

[Redacted] (b) (4)

DDMAC offers the following comments on the proposed patient labeling [Redacted] (b) (4)

General Comments

[Redacted] (b) (4)

Additional Comments

[Redacted] (b) (4)

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/s/

Kathleen Klemm
4/14/2009 03:05:55 PM
DDMAC PROFESSIONAL REVIEWER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 22-372

Name of Drug: SuPrep Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) Concentrate

Applicant: Braintree Laboratories, Inc.

Material Reviewed:

Submission Date(s): July 1, 2008

Receipt Date(s): July 1, 2008

Submission Date of Structure Product Labeling (SPL): July 1, 2008

Type of Labeling Reviewed: SPL. WORD labeling, sent to Matthew Scherer via email on March 18, 2009, was referred to as necessary.

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the sponsor's proposed labeling.

Highlights Section:

- The Highlights section must be limited to one-half page in length (single spaced, one-half inch margins, 8-point font, two-column format). [See 21 CFR 201.57(d)(8)]
- The correct dosage form of this product is [REDACTED]^{(b) (4)}. The drug name, dosage form and route of administration statement should be revised to read: "**SuPrep Bowel Prep Kit**

(sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) **Oral Solution**".
This statement must be in bold type.

- An initial U.S. Approval statement, in bold type, is required. The statement “**Initial U.S. Approval**” followed by a four-digit year must be placed in the line immediately beneath the established name. This statement appears in the WORD version of the label but not in the SPL. The sponsor should be reminded to include this statement. [See 21 CFR 201.57(a)(3)]
- The (b) (4) subsection should be removed.
- Use command language whenever possible (e.g., “...perform appropriate studies to rule out...” rather than (b) (4) throughout the label. Please revise the Highlights (WARNINGS AND PRECAUTIONS) and Full Prescribing Information (5 WARNINGS AND PRECAUTIONS, 8 USE IN SPECIFIC POPULATIONS) sections as necessary.
- The DOSAGE AND ADMINISTRATION subsection is a concise summary of the following items, as applicable: recommended dosage, starting dose, dose range, critical differences among population subsets, monitoring recommendations, clinically significant pharmacological information that affects dosing and special storage and handling information. The proposed subsection is overly detailed and should be revised to be more concise.
- The presentation of adverse event criteria in the ADVERSE EVENTS subsection should be expressed as an incidence rate greater than X%. In the statement “Most common adverse event reactions (b) (4) are abdominal distension...”, (b) (4) should be changed to (b) (4) [See 21 CFR 201.57(a)(11)]
- Insert “.” following the adverse events reporting instructions.
- A revision date, in bold type, must appear at the end of the Highlights. The preferred format is “**Revised: Month Year**” or “**Revised Month/Year**” (e.g., **Revised June 2003** or **Revised 6/2003**). For a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval. [See 21 CFR 201.57(a)(15)].

Full Prescribing Information: Contents:

- A period should be added to the statement: “Sections or subsections omitted from the full prescribing information are not listed”.

Full Prescribing Information (FPI):

- Vague terms and arbitrary categories are used in subsection 8.5 Geriatric Use (b) (4), 12.2 Pharmacodynamics (b) (4) and 12.3 Pharmacokinetics (b) (4). These subsections should be revised by the Medical and Clinical Pharmacology reviewers prior to label negotiations.

- Internal company study titles should be avoided. In the 14 CLINICAL STUDIES subsection, (b) (4)
- The use of bold typeface should be limited to the extent possible. The 16 HOW SUPPLIED /STORAGE AND HANDLING subsection should be revised to remove unnecessary bolding.
- The preferred presentation for cross-references in the Full Prescribing Information is the section heading followed by the numerical identifier in italicized type. In 17 PATIENT COUNSELING INFORMATION, (b) (4)

Recommendations

Unless otherwise noted, the above issues and deficiencies should be conveyed to the sponsor via letter and addressed prior to completion of labeling negotiations.

Matthew Scherer
Regulatory Project Manager

Supervisory Comment/Concurrence:

Cristi Stark, M.S.
Acting Chief, Project Management Staff

Drafted: MCS/3-19-09
Revised/Initialed: CS/3-24-09
Finalized: MCS/3-24-09
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

Matthew Scherer
3/24/2009 01:31:39 PM
CSO

Cristi Stark
3/25/2009 07:33:20 AM
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 3/24/2009

TO: Matthew Scherer, Regulatory Project Manager
Jasmine Gatti, M.D., Medical Officer
Division of Gastrointestinal Products

FROM: Khairy Malek, M.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA #: 22-372

APPLICANT: Braintree Laboratories

DRUG: SuPrep (BLI-800 Oral Sulfate Solution)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Bowel cleansing prior to colonoscopy

CONSULTATION REQUEST DATE: October 22, 2008

DIVISION ACTION GOAL DATE: May 1, 2009

PDUFA DATE: May 1, 2009

I. BACKGROUND:

Inspections of protocols BLI-800-301 and BLI-800-302 were conducted in support of NDA 22-372. The studies are designed to compare the efficacy and safety of BLI-800 (oral sulfate solution) to MoviPrep, which is FDA approved, for bowel preparation before colonoscopy examination in subjects scheduled to undergo colonoscopy for a routine indication.

The two protocols inspected for this NDA differ in the way the drug is given. In protocol 301, the two doses of the MoviPrep, one liter each, or the new oral sulfate drug, 6 ounces each, are given at approximately 6 and 7 PM on the day before colonoscopy. In protocol 302, there is a split dose: a 6-ounce bottle of BLI-800 is given at approximately 6 PM on the day before colonoscopy, and a second 6-ounce dose is given the next day at approximately 6 AM. The MoviPrep is also given, one liter at approximately 6 PM and the second liter at about 6 AM on the morning of the colonoscopy. The two inspected protocols are as follows:

Protocol BLI-800-301, entitled “A Safety and Efficacy Evaluation of BLI- 800 Oral Sulfate Solution vs. “MoviPrep” as Bowel Cleansing Preparations in Adult Subjects”; and

Protocol BLI-800-302, entitled “A Safety and Efficacy Evaluation of BLI-800 Oral Sulfate Solution vs. “MoviPrep” as Split-Dose Bowel Cleansing Preparations in Adult Subjects.”

II. RESULTS:

Name of CI Location	Protocol # and # of Subjects:	Inspection Dates	Final Classification
Richard Chasen, M.D. 7350 Van Dusen Road, Suite 360 Laurel, MD 20707	Protocol 301 75 Subjects	December 11, 2008 to January 6, 2009	VAI
Steven Duckor, M.D. 2617 East Chapman Ave. Suite 302 Orange, CA 92801	Protocol 302 46 Subjects	December 18, 2008 to January 12, 2009	VAI
Dennis Riff, M.D. 1211 West La Palma Ave., Suite 602 Anaheim, CA 92801	Protocol 302 80 Subjects	January 7 to 9, 2009	VAI
Lawrence Wruble, M.D. 8000 Wolf River Road, Suite 200 Germantown, TN 38138	Protocol 302 40 Subjects	January 14 and 15, 2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

1. Richard Chasen, M.D.-Site # 3

Maryland Digestive Disease Research, 7350 Van Dusen Road, Suite 360
Laurel, MD 20707

- a. What was inspected: At this site, the field investigator reviewed the records of 31 subjects, comparing source documents with the data reported to the FDA.
- b. General observations/commentary: The inspection revealed protocol violations: Five subjects (four of whom had a tubal ligation) did not have a urine pregnancy test before taking the investigational drug; and in some cases, the drug kits were not dispensed in order to the subjects with the lower number given first as the protocol specifies.
- c. Assessment of data integrity: These violations would not affect the validity of the data, and the data from this site can be used in support of the NDA

2. Steven Duckor, M.D.-Site # 13

Advanced Clinical Research Institute, 2617 E Chapman Ave., Suite 302
Orange, CA 92869

- a. What was inspected: The field investigator reviewed the records of 25 subjects and all of the informed consent documents.
- b. General observations/commentary: The inspection revealed that the clinical investigator (CI) did not report to the sponsor an adverse reaction in 5 subjects out of the 25 reviewed. The adverse reaction was an elevation in serum uric acid between Visit 1 and Visit 2. There was also an inaccurate record in that for subject # 13026, source documents described “bleeding from hemorrhoids” while the electronic case report form (eCRF) documented “GI bleeding.”
- c. Assessment of data integrity: These violations would not affect the reliability of the data, and the data from this site can be used in support of the NDA.

3. Dennis Riff, M.D., Site 15

Advanced Clinical Research Institute, 1211 West La Palma Ave., Suite 602
Anaheim, CA 92801

- a. What was inspected: An audit of 40 subjects’ records was performed.
- b. General observations/commentary: One protocol violation was observed in that

one subject was given the test drug and had a colonoscopy performed before the site received the screening laboratory tests.

- c. Assessment of data integrity: The data generated from this site appear reliable and can be used in support of the NDA.

4. Lawrence Wruble, M.D., Site # 20
Memphis Gastroenterology Group, 8000 Wolf River Blvd., Suite 200
Germantown, TN 38138

- a. What was inspected: The field investigator reviewed all the subjects' records at this site.
- b. General Observations/Commentary: At this site two SAEs were observed: Subject # 13 died from respiratory distress and multiple organ failure, weeks after colon resection. An adenoma was discovered during colonoscopy. The other SAE was observed by the site during their preparation for the FDA inspection: Subject # 30 had a complication of the colonoscopy as the subject suffered severe right lower quadrant abdominal pain on the day of the colonoscopy. A CT scan showed intra-peritoneal air. The subject has been scheduled to have a right hemicolectomy because of non-resectable polyps and the perforation repair was done during the procedure. During randomization, this subject (# 30) was included in the "MoviPrep" group. The inspection also revealed a protocol violation in that subject # 006 was given the study drug before the screening laboratory tests were done. Also, there was an inaccurate record in that, during the checking for inclusion criteria, the pregnancy test was marked as "done" for 2 male subjects.
- c. Assessment of data integrity: These violations would not affect the reliability of the data. The data from this site can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from all 4 sites appear valid and can be used in support of the NDA.

Khairy Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Constance Lewin
3/24/2009 12:57:39 PM
MEDICAL OFFICER
Entered into DFS on behalf of Dr. Khairy Malek.

January 16, 2009

Memo to: Jasmine Gatti, MD, Medical Officer
Division of Gastrointestinal Drug Products

From: Ann Corken Mackey, RPh, MPH, Safety Evaluator
Office of Surveillance and Epidemiology

Re: Bowel preparations and elevated creatine kinase

Control# 2008-2039

I am responding to your request of December 18, 2008 regarding reports of elevated Creatine Kinase (CK) associated with bowel preparations Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) and Moviprep (polyethylene glycol [PEG]) that were identified in the sponsor submission (NDA 22-372). As per your request, the Adverse Event Reporting System (AERS) database was searched for reports of elevated CK associated with other products used as bowel preparations (sodium phosphate, PEG) as well as concomitant medications that may be given for a procedure (e.g., propofol, midazolam, fentanyl, demerol).

AERS was searched for cases of elevated CK associated with sodium phosphate, PEG, midazolam, propofol, demerol and fentanyl. The search found no cases reported for PEG, propofol, or demerol. The search identified one case associated with **sodium phosphate oral solution** use for bowel cleansing before colonoscopy involving a 79yo female who became acidotic and died (pt had increased CK, troponin, phosphorus, sodium, creatinine, glucose, SGOT and decreased calcium and magnesium). The search identified one case associated with **sodium phosphate tablets and midazolam** use before colonoscopy involving a 46yo female who experienced a myocardial infarction shortly after her procedure (patient also using baclofen which is known to cause increased CK per reporter). As discussed, a search of AERS for fentanyl identified 61 reports (note raw data, duplicates could exist). None of these patients were using fentanyl for a colonoscopy; the indications for use included chronic pain associated with malignancy or short term use for surgery. Approximately 30% of the cases were associated with an overdose of fentanyl and other substances. Most of the patients had underlying conditions known to increase CK, including rhabdomyolysis, myocardial infarction, malignant hyperthermia, myalgia, etc. At least one patient's CK returned to normal when a concomitant statin drug was discontinued (statin drugs are known to increase CK).

In reviewing the study reports you provided, it was noted that a couple of patients who experienced increased CK were receiving statin drugs concomitantly, this could have played a role. Most of the investigators stated that the increases in CK were not clinically significant; it may be reasonable to ask the sponsor to explain these cases (including any events experienced because of the increased CK).

Ann Corken Mackey

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/s/

Ann Corken
3/26/2009 04:05:48 PM
DRUG SAFETY OFFICE REVIEWER

Lanh Green
3/26/2009 04:55:48 PM
DRUG SAFETY OFFICE REVIEWER

DSI CONSULT: Request for Clinical Inspections

Date: October 22, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Khairy Malek, M.D., Medical Officer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Jasmine Gatti, M.D., Medical Reviewer, HFD-180*

From: *Matthew Scherer, Regulatory Project Manager, HFD-180*

Subject: **Request for Clinical Site Inspections**
Suprep (sodium sulfate, potassium sulfate, magnesium sulfate)
Oral Solution

I. General Information

Application#: NDA 22-372

Applicant/ Applicant contact information (to include phone/email): Matthew Scherer, Regulatory Project Manager, 301-796-2307 and Jasmine Gatti, Medical Officer, 301-796-2074.

Drug Proprietary Name: Suprep

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Bowel cleansing prior to colonoscopy

PDUFA: May 1, 2009

Action Goal Date: May 1, 2009

Inspection Summary Goal Date: March 18, 2009

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 3 Richard Chasen, M.D. Maryland Digestive Disease Research, LLC 7350 Van Dusen Road, Suite 360 Laurel, MD 20707 PH: 240-554-0384 or 240-554-0135 Fax: 240-554-0131	BLI800-301	75	Bowel cleansing prior to colonoscopy
Site 13 Steven Duckor, M.D. Advanced Clinical Research Institute 2617 East Chapman Ave. Suite 302 Orange, CA, 92869 PH: 714-633-1823 Fax: 714-532-4891	BLI800-302	46	Bowel cleansing prior to colonoscopy
Site 15 Dennis Riff, M.D. Advanced Clinical Research Institute 1211 West La Palma Avenue, Suite 602 Anaheim, CA 92801 PH: 714-778-1300 Fax: 1-714-778-0667	BLI800-302	80	Bowel cleansing prior to colonoscopy
Site 20 Lawrence Wruble, M.D. Memphis Gastroenterology Group 8000 Wolf River Blvd - Suite 200 Germantown, TN 38138 PH: 901-747-3630 Fax: 901-747-0176	BLI800-302	40	Bowel cleansing prior to colonoscopy

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*

- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): see summary, and adverse events

International Inspections:

not applicable

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

not applicable

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

No specific data verification

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Matthew Scherer at 301-796-2307 or Jasmine Gatti at 301-796-2074.

Concurrence: (as needed)

_____ *John Hyde* _____ Medical Team Leader
_____ *Jasmine Gatti* _____ Medical Reviewer
_____ _____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results? **See below***
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites? **See below***
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites? **TBD***
- *Are there concerns that the data may be fraudulent or inconsistent? **Not at this point.***
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct? **Not at this point.***
- *Is this a new molecular entity or original biological product? **No***
- *Is the data gathered solely from foreign sites? **No***
- *Were the NDA studies conducted under an IND? **Yes***

Summary of Rationale for Site Selection

We chose site 3 (n=75) and 15 (n=80) due to the highest enrollments.

We chose sites 13 and 20 based on efficacies of treatment of 95% or greater. They both also had fewer adverse events (6 or less) and one had a severe adverse event of death (site 20).

Site 13 was also chosen because it may be affiliated with the other site in California.

Site 20 was also chosen because it is in a less populated area.

We request that the inspectors check confidentiality of patient data since some patient labs submitted to the FDA showed patient names.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Matthew Scherer
11/5/2008 10:47:32 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-372 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Suprep
Established Name: sodium sulfate, potassium sulfate and magnesium sulfate
Strengths:

Applicant: Braintree Laboratories, Inc.
Agent for Applicant (if applicable):

Date of Application: July 1, 2008
Date of Receipt: July 2, 2008
Date clock started after UN:
Date of Filing Meeting: August 21, 2008
Filing Date: August 31, 2008
Action Goal Date (optional): User Fee Goal Date: May 2, 2009

Indication(s) requested: Gastrointestinal lavage prior to colonoscopy

Type of Original NDA: (b)(1) X (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.) NA

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
The index associated with the initial submission was insufficient, however, the sponsor submitted a revised index which is acceptable.
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, _____ Years NO X

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO

- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 74,808

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 3-26-07 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) SPA letter: NO X
 If yes, distribute letter and/or relevant minutes before filing meeting.
 SPA submitted but no agreements. SPA meeting minutes: 11-8-07

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
 If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
 Was the PI submitted in PLR format? YES X NO
 If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8-21-08

NDA #: 22-372

DRUG NAMES: Suprep

APPLICANT: Braintree Laboratories, Inc.

BACKGROUND:

SUPREP® BOWEL PREP KIT (sodium sulfate, potassium sulfate and magnesium sulfate for oral solution) is intended for bowel cleansing prior to colonoscopy. The product is supplied as a liquid concentrate in two 6 ounce bottles, along with a mixing cup which is used for diluting the product with water prior to drinking; dilution to 16 ounces is required, (b) (4)

The contents of each of the two bottles are to be taken at prescribed intervals prior to colonoscopy. This product, which was studied under IND 74,808, is being filed by Braintree as a 505(b)(1) application.

The proposed product contains three active ingredients: sodium sulfate and magnesium sulfate, which have been approved for use in other products, and potassium sulfate, which is a new active ingredient. However, it should be noted that both sulfate ions and potassium ions function as active moieties, as has been the case in other approved applications.

Tentative list of ATTENDEES:

Anne Pariser, Acting Deputy Direct, Division of Gastroenterology Products
John Hyde, Medical Team Leader, Division of Gastroenterology Products
Jasmine Gatti, Medical Officer, Division of Gastroenterology Products
David Joseph, Acting Supervisory Pharmacologist, Division of Gastroenterology Products
Tamal Chakraborti, Pharmacologist, Division of Gastroenterology Products
Mike Welch, Deputy Director, Biostatistics
Jane Bai, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Marie Kowblansky, Pharmaceutical Assessment Leader, Office of New Drug and Quality Assessment
Tarun Mehta, CMC Reviewer, Office of New Drug and Quality Assessment
Matthew Scherer, Regulatory Project Manager, Division of Gastroenterology Products
Roland Girardet, Regulatory Project Manager, Division of Gastroenterology Products
Eddie Ng, Pharmacologist, Division of Gastroenterology Products

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:

Reviewer

Jasmine Gatti
NA
Mike Welch, Shahla Farr
Tamal Chakraborti
NA
Tarun Mehta

Environmental Assessment (if needed): NA
 Biopharmaceutical: Jane Bai
 Microbiology, sterility: NA
 Microbiology, clinical (for antimicrobial products only): NA
 DSI: TBD
 OPS: NA
 Regulatory Project Management: Matthew Scherer
 Other Consults: DDMAC, DMEPA are TBD

Per reviewers, are all parts in English or English translation? YES X NO
 If no, explain:

CLINICAL FILE X REFUSE TO FILE
 • Clinical site audit(s) needed? TBD YES X NO
 If no, explain:
 • Advisory Committee Meeting needed? YES, date if known _____ NO X
 • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE
 STATISTICS N/A FILE X REFUSE TO FILE
 BIOPHARMACEUTICS FILE X REFUSE TO FILE
 • Biopharm. study site audits(s) needed? YES NO X
 PHARMACOLOGY/TOX N/A FILE X REFUSE TO FILE
 • GLP audit needed? YES NO X
 CHEMISTRY FILE X REFUSE TO FILE
 • Establishment(s) ready for inspection? YES X NO
 • Sterile product? YES NO X
 If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:
 Any comments: NA

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Matthew C Scherer
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Matthew Scherer
9/8/2008 12:56:23 PM
CSO