

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022372Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022372

SUPPL # NA

HFD # 180

Trade Name Suprep Bowel Prep Kit

Generic Name sodium sulfate, potassium sulfate, magnesium sulfate

Applicant Name Braintree Laboratories, Inc.

Approval Date, If Known Expected March 16, 2010

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

**Sodium Sulfate:**

NDA# 021881	Moviprep
NDA# 018983	Colyte, Colyte – Flavored, and Colyte with Flavor Packs
NDA# 019011	Golytely

**Magnesium Sulfate:**

NDA# 020577	Elliot’s B Solution
NDA# 019316	Magnesium Sulfate
NDA# 020488	Magnesium Sulfate in Dextrose 5% in Plastic Container
NDA# 020309	Magnesium Sulfate in Plastic Container

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)

IF “YES,” GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

BLI800-301  
BLI800-302

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

BLI800-301 YES  NO   
BLI800-302 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

BLI800-301 YES  NO   
BLI800-302 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

BLI800-301

BLI800-302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (BLI800-301) !  
!  
IND # 074808 YES  ! NO   
! Explain:

Investigation #2 (BLI800-302) !  
!  
IND # 074808 YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2 !

YES   
Explain:

!  
! NO   
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Drafted by: Matthew Scherer  
Title: Regulatory Project Manager  
Date: 3-11-10

Name of person completing form: John Hyde  
Title: Medical Team Leader  
Date: 3-11-10

Name of Office/Division Director signing form: Donna Griebel  
Title: Director, Division of Gastroenterology Products  
Date: 3-15-10

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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/s/

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MATTHEW C SCHERER  
03/25/2010

DONNA J GRIEBEL  
08/04/2010

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022372 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Suprep Bowel Prep Kit Established/Proper Name: sodium sulfate, potassium sulfate, magnesium sulfate Dosage Form: Oral solution		Applicant: Braintree Laboratories, Inc. Agent for Applicant (if applicable):
RPM: Matthew Scherer		Division: Division of Gastroenterology Products
<p><b>NDA:</b> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2) Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p style="text-align: center;"><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b><u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date was originally <u>May 2, 2009</u> and was extended to <u>August 2, 2009</u> due to submission of a major amendment</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>2</sup></p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>          Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes, date
<p>❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	8-5-10
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s): Approval, 8-5-10
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NA

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	NA
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	NA 5-6-10, 1-15-10, 8-10-09, 4-16-09
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 3-25-09 <input checked="" type="checkbox"/> DMEDP 4-16-09 (combined with TN review) <input checked="" type="checkbox"/> DRISK 7-15-10, 8-7-09 <input checked="" type="checkbox"/> DDMAC 6-9-10, 4-14-09 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	9-8-08
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>April 29, 2009</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	Pediatric record included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	7-21-10, 4-9-10, 11-20-09, 7-30-09, 7-22-09, 6-23-09, 5-27-09, 5-22-09, 4-29-09, 4-28-09, 4-14-09, 4-13-09, 3-27-09, 3-3-09, 2-18-09, 2-6-09, 2-5-09, 12-5-08, 11-17-08,

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 12/4/09

	11-12-08, 9-12-08, 7-16-08
❖ Internal memoranda, telecons, etc.	7-29-09
❖ Minutes of Meetings	
• Pre-Approval Safety Conference ( <i>indicate date of mtg; approvals only</i> )	N/A
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> 8-28-09
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	N/A
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	No meeting
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> 3-26-07
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) ( <i>indicates dates</i> )	None
❖ Advisory Committee Meeting(s)	No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	None
Division Director Summary Review ( <i>indicate date for each review</i> )	8-5-10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	6-28-10
PMR/PMC Development Templates ( <i>indicate total number</i> )	8-3-10
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	None. CDTL Review from Clinical Team Leader included in Summary Memos
• Clinical review(s) ( <i>indicate date for each review</i> )	8-19-09
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See page 25 of the 8-19-09 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	10-26-09, 10-14-09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo (<i>indicate date</i>)</li> <li>• REMS Notification Letter</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	Included (submitted 7-29-10) 6-22-10 6-22-10 3-26-09

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 12/4/09

❖ DSI Clinical Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	Letters: 5-5-09, 4-10-09 (2), 3-27-09 Review: 3-24-09
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	None
Statistical Review(s) <i>(indicate date for each review)</i>	7-7-09
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	4-10-09
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	None
• Supervisory Review(s) <i>(indicate date for each review)</i>	None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	3-6-09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	No carc
❖ ECAC/CAC report/memo of meeting	None
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	8-6-09, 7-16-09, 8-25-08
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	4-7-09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See p. 16 of the 8-6-09 CMC review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> )	Date completed: 4-29-09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

## Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ADRA.

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/s/  
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MATTHEW C SCHERER

08/05/2010

**Scherer, Matthew**

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**From:** Scherer, Matthew  
**Sent:** Wednesday, July 21, 2010 10:54 AM  
**To:** 'Caballero, Vivian'  
**Cc:** 'Walsh, Claire'; 'mvcleveland@braintreelabs.com'  
**Subject:** NDA 022372 (Suprep) labeling and REMS/MG comments

**Attachments:** SuPrep PI - for revision - 7-21-10.pdf; electrolyte shift data and comment for PI Sec 6.pdf

Dear Ms. Caballero,

Attached, please find an annotated package insert that includes the changes sent via email on June 28, 2010 as well as additional requested revisions [redacted] (b) (4) and inclusion of a Medication Guide.



SuPrep PI - for revision - 7-2...

Also attached, please find a revised electrolyte shift table (Table 2) with an accompanying comment to be added to the package insert. Note that this table includes a selection of data from study 302 (the split-dose regimen study). Please reformat so that it fits logically into the package insert in Section 6 Adverse Reactions, 6.1 Clinical Studies Experience.



electrolyte shift data and com...

Also, we have the following requests for revision to your REMS document (submitted June 30, 2010):

- 1) Remove the [redacted] (b) (4).
- 2) Please revise the REMS Goal to remove the [redacted] (b) (4).
- 3) Please revise the REMS Elements, Medication Guide as follows:  
[redacted] (b) (4)  
[redacted]  
[redacted]

Furthermore, for the Medication Guide (submitted June 30, 2010), [redacted] (b) (4) the "Patient Instructions for Use Booklet"

Please ensure that all patient labeling, including the Medication Guide and Patient Instruction for Use, are consistent with the Package Insert.

Please submit all revised labeling (package insert, Medication Guide, REMS Goal and Elements, container/carton/booklet) to the NDA.

Best regards,

**Matthew C. Scherer**  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODEIII  
Ph: 301-796-2307  
Fax: 301-796-9905

10903 New Hampshire Avenue  
Building 22, Room 5137  
Silver Spring, MD 20993

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MATTHEW C SCHERER

07/21/2010

## Scherer, Matthew

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**From:** Scherer, Matthew  
**Sent:** Monday, June 28, 2010 3:19 PM  
**To:** 'Caballero, Vivian'  
**Cc:** 'cwalsh@braintreelabs.com'  
**Subject:** Suprep (NDA 022372) requested revisions to Med Guide and PI

**Attachments:** revised MG for BLI 062810.pdf; SuPrep PI for BLI 062810pdf.pdf

Dear Ms. Caballero,

Attached, please find DGP's initial revisions to your proposed Medication Guide for Suprep, submitted May 27, 2010.

Also attached, are additional requested revisions to the Suprep package insert, shown in track changes as much as possible.

Please note, upon further review, we may have additional requests for labeling changes.



revised MG for BLI 062810.pdf ... SuPrep PI for BLI 062810pdf.pdf...

Best regards,

**Matthew C. Scherer**  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODEIII  
*Ph: 301-796-2307*  
*Fax: 301-796-9905*

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MATTHEW C SCHERER

06/29/2010



NDA 022372

**INFORMATION REQUEST**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) oral solution.

We also refer to the May 20, 2010, teleconference between Braintree Laboratories, Inc. and the Division of Gastroenterology Products where we indicated that a Medication Guide would be required before we could consider approving this NDA.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) to ensure that the benefits of the drug outweigh the risks of fluid and electrolyte disturbances that can lead to serious adverse events, including cardiac arrhythmias, seizures and renal impairment.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of SUPREP Bowel Prep Kit. FDA has determined that SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) oral solution is a product for which patient labeling could help prevent serious adverse effects.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4)

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include an evaluation of patients’ understanding of the serious risks of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4)

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022372**  
**PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022372**  
**PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, MD  
Director  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**APPENDIX A: MEDICATION GUIDE REMS TEMPLATE**

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name  
Address  
Contact Information

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide**

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

**B. Timetable for Submission of Assessments**

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, 18 months, three years and seven years from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

**APPENDIX B:**

**REMS SUPPORTING DOCUMENT TEMPLATE  
MEDICATION GUIDE REMS**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Medication Guide
  - b. Describe in detail how you will comply with 21 CFR 208.24.
  - c. Timetable for Submission of Assessments of the REMS (for products approved under an NDA)
5. REMS Assessment Plan (for products approved under an NDA)
6. Other Relevant Information

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DONNA J GRIEBEL

06/22/2010

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Matthew Scherer, Div Gastroenterology Products 301-796-2307
------------------------------	---

REQUEST DATE 5/28/10	IND NO.	NDA/BLA NO. 22372	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Suprep Bowel Prep Kit	PRIORITY CONSIDERATION High priority	CLASSIFICATION OF DRUG Cathartic/laxative	DESIRED COMPLETION DATE June 11, 2010
---------------------------------------	---	--	--

NAME OF FIRM: Braintree Laboratories, Inc.	PDUFA Date: August 2, 2009
---	----------------------------

## TYPE OF LABEL TO REVIEW

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION  Note: PI, PPI and Carton/container have already been reviewed by DDMAC. This consult is for the review of the recently submitted Med Guide
---	--	---

**EDR link to submission:**

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

**COMMENTS/SPECIAL INSTRUCTIONS:**  
Mid-Cycle, Labeling and Wrap-Up Meetings: occurred in past. DDMAC will be invited to any future meetings where labeling will be discussed.

This NDA is significantly past the PDUFA date. DGP has determined that is cannot be approved without a Medication Guide. The remainder of the labeling is substantially complete; (b) (4)  
(b) (4) Also, the electrolyte shift table in the PI, section 6 will be revised.

I will forward the proposed Med Guide and a link to the most recent PI in a separate email. Please contact Matt Scherer (RPM, x6-2307) with any questions.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND
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MATTHEW C SCHERER

05/28/2010



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MATTHEW C SCHERER

05/28/2010



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) oral solution.

We have the following requests for information. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a list of patients (with patient identified, study number and treatment assignment) who developed low serum bicarbonate on study and were normal at baseline.
  - a. For these patients, provide the following information for baseline visit, Visit 2, and follow-up:
    - i. serum sodium
    - ii. serum potassium
    - iii. serum chloride
    - iv. serum BUN and creatinine
    - v. serum calcium
    - vi. serum uric acid
    - vii. AND calculated anion gap
  - b. Additionally, for these patients, provide a list of concomitant medication at baseline and at the follow-up visit.
2. For the following lab abnormalities detected at Visit 2, in patients who did not have an abnormal laboratory finding at baseline, document the patients with the abnormalities and whether the abnormality had resolved at the follow up visit. In addition, identify patients who were normal at baseline and Visit 2, but developed the abnormality at the follow-up visit. Provide a list of these patients, along with the associated laboratory values at baseline visit, Visit 2, and follow-up. In addition, provide a list of their baseline concomitant medications.
  - a. hypocalcemia
  - b. hypercalcemia
  - c. hyperuricemia
  - d. low serum bicarbonate
  - e. hyperbilirubinemia, total and/or direct
  - f. elevated serum creatinine

3. Provide your assessment of the etiology of the elevated serum calcium levels observed in the two trials.
4. Provide your assessment of the etiology of the elevated bilirubins observed in the trials, including the elevated direct bilirubins.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
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Submitter Name

Product Name

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NDA-22372

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SUPREP BOWEL PREP KIT

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/s/  
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RICHARD W ISHIHARA  
04/09/2010

## Scherer, Matthew

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**From:** Scherer, Matthew  
**Sent:** Friday, November 20, 2009 10:23 AM  
**To:** 'Caballero, Vivian'  
**Subject:** Revised Suprep label (NDA 22-372)

**Attachments:** SuPrep PI for BLI 112009.pdf; SuPrep PI sent to BLI 112009.doc

Dear Ms. Caballero,

Please see the attached files, which include additional requested revisions to the SUPREP Bowel Prep Kit package insert. Please note that in we are requesting that you put together a table of electrolyte values in 6.1 (please see the specific section for details). Also note that the label is a work in progress and we may have additional revisions.



SuPrep PI for BLI 112009.pdf (...  
SuPrep PI sent to BLI 112009.d...

Best regards,

**Matthew C. Scherer**  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODEIII  
*Ph: 301-796-2307*  
*Fax: 301-796-9905*

10903 New Hampshire Avenue  
Building 22, Room 5137  
Silver Spring, MD 20993

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

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MATTHEW C SCHERER

11/20/2009

## REQUEST FOR CONSULTATION

TO (Office/Division):  
Devi Kozeli, DCRP

FROM (Name, Office/Division, and Phone Number of Requestor):  
Matthew Scherer, DGP

DATE 9-3-09	IND NO.	NDA NO. 022372	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 7-2-08
NAME OF DRUG SuPrep Bowel Prep Kit		PRIORITY CONSIDERATION urgent (PDUFA = 8-2-09)	CLASSIFICATION OF DRUG cathartic/laxative	DESIRED COMPLETION DATE update: prior to 9-10-09 completion: 9-24-09

NAME OF FIRM: Braintree Labs, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input checked="" type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

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|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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**COMMENTS / SPECIAL INSTRUCTIONS:** 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?
2. Please recommend an intervention for patients who have documented elevations in creatinine after treatment.
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.

Please contact Donna Griebel (Division Director), John Hyde (Team Leader – o leave from 9-9-09 to 9-25-09), Jasmine Gatti (Medical Officer) or Matthew Scherer (RPM) if you have any questions.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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MATTHEW C SCHERER

09/04/2009

## REQUEST FOR CONSULTATION

TO (Office/Division):  
**Eric Frimpong, Division of Biostatistics VI**

FROM (Name, Office/Division, and Phone Number of Requestor): **Matthew Scherer, RPM, Div of Gastroenterology**

DATE <b>9-1-09</b>	IND NO.	NDA NO. <b>22-372</b>	TYPE OF DOCUMENT	DATE OF DOCUMENT <b>1-22-09, 6-11-09</b>
NAME OF DRUG <b>SuPrep Bowel Prep Kit</b>		PRIORITY CONSIDERATION <b>high</b>	CLASSIFICATION OF DRUG <b>cathartic/laxative</b>	DESIRED COMPLETION DATE <b>9-8-09</b>

NAME OF FIRM: **Braintree Labs, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input checked="" type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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#### IV. DRUG SAFETY

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|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
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**COMMENTS / SPECIAL INSTRUCTIONS:** As discussed at the meeting between the DGP SuPrep review team and Antonio Paredes, Eric Frimpong and Benjamin Neustifter, DGP is requesting your assistance in evaluating outlier Chemistry Lab values for patients in the phase 3 studies (301 and 302) submitted for NDA 22-372 (SuPrep). The extended PDUFA date (8-2-09) has passed. As discussed, we are interested in demographic information for trial patients with abnormal creatinines (high), BUN (high), Sodium (hi/lo), Uric Acid (high), Calcium (hi/lo), Bicarbonate (low), Chloride (hi/lo), Serum Osmolality (hi/lo) and Magnesium (high), Phosphorus (hi/lo), and Potassium (hi/lo). The datasets and define files are available in the EDR - specific links have been sent to you in a separate email. Please indicate which of these patients are "High Risk" and if there are any correlatable outlying features in age (>65), weight (obesity), and adverse events (gastrointestinal symptoms, cardiac, or renal).

Please contact Matthew Scherer (RPM), Jasmine Gatti (MO) or John Hyde (MOTL) if you require any further clarification.

Thanks, Matt

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MATTHEW C SCHERER

09/04/2009

## **MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** August 28, 2009  
**MEETING TIME:** 11:00 am to 1:00 pm  
**LOCATION:** White Oak Campus, Conference Room CSU 2047  
**APPLICATION:** NDA 022372  
**DRUG NAME:** SUPREP Bowel Prep Kit  
**TYPE OF MEETING:** Regulatory Briefing

**MEETNIG CHAIR:** John Jenkins, M.D., Director, Office of New Drugs

**MEETING RECORDER:** Matthew Scherer, M.B.A., DGP

### **REGULATORY BRIEFING PANEL**

Doug Throckmorton, M.D., Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research  
John Jenkins, M.D., Director, Office of New Drugs  
RADM Sandy Kweder, M.D., Deputy Director, Office of New Drugs  
Charles Ganley, M.D., Director, Office of Non-Prescription Drugs  
Jogarao Gobburu, M.D., Director, Office of Clinical Pharmacology, Division of Pharmacometrics  
Solomon Sobel, M.D., Associate Director, Science and Research Staff

### **BACKGROUND**

New Drug Application (NDA) 022372 was submitted on July 1, 2008 by Braintree Laboratories, Inc. This NDA sought approval for the SUPREP Bowel Prep Kit (Suprep) for cleansing of the colon prior to colonoscopy. Suprep is an osmotic laxative containing sodium sulfate, potassium sulfate and magnesium sulfate. The product is administered [REDACTED] (b) (4) as a split dose, with half the dose taken the night before endoscopy and the second dose administered the morning of endoscopy (2-Day regimen). The safety evaluation in the studies submitted to support approval included CBC, serum chemistry, physical examination and vital signs at screening and at the time of presentation for endoscopy (which was after taking the full dose for the bowel prep). On Day 30 after endoscopy, the CBC and chemistry were repeated. Adverse events were collected both on the day of colonoscopy and on Day 30.

The oral sodium phosphate products used for bowel cleansing in preparation for endoscopy were recently the subject of class labeling under FDAAA. The labels were revised to include a boxed warning that states:

#### **“WARNINGS**

There have been rare, but serious reports of acute phosphate nephropathy in patients who received oral sodium phosphate products for colon cleansing prior to colonoscopy. Some

cases have resulted in permanent impairment of renal function and some patients required long-term dialysis. While some cases have occurred in patients without identifiable risk factors, patients at increased risk of acute phosphate nephropathy may include those with increased age, hypovolemia, increased bowel transit time (such as bowel obstruction), active colitis, or baseline kidney disease, and those using medicines that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]). See **WARNINGS.**”

In addition the nonprescription oral sodium phosphate products used for bowel prep have been removed from the OTC market.

While Suprep is a sulfate-based bowel preparation and the oral sodium phosphate products are phosphate-based, they are all osmotic laxatives. The Division of Gastroenterology Products (DGP) has concerns that Suprep may have risks that are present with other osmotic laxatives, including renal impairment, cardiac arrhythmias, colonic mucosal ulcers, and ischemic colitis.

DGP seeks the advice of the Regulatory Briefing Panel whether an additional safety study should be conducted pre-approval to provide a more intensive safety evaluation of Suprep or if a required postmarketing safety study would be a more appropriate means to acquire additional safety information.

### **FDA PRESENTATIONS**

1. Regulatory History of Cathartics and Background of Recent Approvals and Safety Issues: Joyce Korvick, M.D., M.P.H., Deputy Director of Safety
2. Pharmacology/Toxicology: Tamal Chakraborti, Ph.D., Pharmacologist
3. Clinical Pharmacology: Jane Bai, Ph.D., Pharmacology Reviewer
4. Clinical Safety: Jasmine Chen Gatti, M.D., Medical Officer
5. Issues for Consideration: John Hyde, Ph.D., M.D., Medical Team Leader

The slide presentations are attached to these minutes, below.

### **QUESTIONS FOR DISCUSSION**

1. Should safety investigations be required pre-approval to provide additional safety data for Suprep?

If yes, should these investigations include:

- a. Repeat of active-controlled Phase 3 trials with additional safety monitoring?
- b. Large, uncontrolled safety study?

2. If no further investigations are required pre-approval, should there be Post-Marketing Requirements (PMRs) for additional safety data?

If yes, should these PMRs include:

- a. Repeat of active-controlled Phase 3 trials with additional safety monitoring?
  - b. Large, uncontrolled safety study?
3. If repeated Phase 3 trials are required (either pre- or post-marketing), what study design elements should be required:
    - a. ECGs?
    - b. U/A?
    - c. Orthostatic vital signs?
    - d. More intensive safety evaluation between the day of colonoscopy and Day 30? If so, what testing and when?
    - e. Baseline blood tests closer to the beginning of the prep?
    - f. Monitoring beyond 30 days?
    - g. Other?
  4. If a large safety study is required (either pre- or post-marketing), what should be specified regarding:
    - a. Size?
    - b. Duration?
    - c. Type and intensity of safety monitoring?
  5. If Suprep is approved without additional pre-market studies, how should this new osmotic laxative be labeled regarding safety?

### **MEETING DISCUSSION**

Dr. Jenkins began the discussion noting that DGP had to consider that a Special Protocol Assessment (SPA) agreement was made and that the protocol's safety monitoring deficiencies should have been addressed at that time.

Dr. Throckmorton commented that DGP is stuck between what was said in the SPA agreement and the present. It appears that at the time of the SPA, we had significant understanding of fluid shifts. He recommended that, to determine long-term clinical effects, the safety assessment should focus on lab results at 30 days; interim values are inconsequential. The additional data would certainly be nice to have, but DGP needs an argument for why it is needed to properly label the drug.

Dr. Jenkins mentioned that, in order to require additional safety data pre-approval, DGP will have to explain why the SPA agreement is no longer valid. The law states that science should drive that decision; the SPA agreement can be ignored if science changes, but not solely because an opinion changes. A SPA agreement reflects the Agency's thinking at the time and is not a guarantee. If the Agency erred in making the agreement, we should not be held to it. He added

that we now have FDAAA and can require postmarketing trials, however, we should not substitute postmarketing data if we really need it prior to approval.

Dr. Cox notes that requiring safety investigations allows us to bound the risk prior to approval. He recommended studying a “couple thousand patients” to better characterize safety. Most patients should get the test drug, but use of a control group is important to interpret the results. A 3:1 randomization might be appropriate. The patient population for bowel preps has lots of underlying disease. DGP may want to increase monitoring for special populations. He recommended that DGP require another study pre-approval.

Dr. Gobburu commented that more safety data is needed before an approval. He recommended that the sponsor also study additional doses.

### **ATTACHMENTS**

The slide presentations are attached.



# Bowel Cleansing Products Background & Recent Safety Issues

Joyce Korvick, MD, MPH  
Deputy Director for Safety  
Division of Gastroenterology Products

Thanks to Dr. Eric Brodsky and Ann Corken-Mackey



# Post-Market Safety of Bowel Preparations

- Background Approved Bowel Preps
- Clinical Trials safety data from previous reviews
- Post-Market Safety Review
  - Sodium phosphate oral solution (SPOS)
  - Sodium phosphate tablet (SPT)
  - Polyethylene glycol (PEG)
- Oral Sodium Phosphates
  - Recent FDAAA Safety Labeling changes
  - PMR study



# Bowel Cleansing Products

## Oral Sodium Phosphate Preps

- Oral sodium phosphate solution (30g Na<sub>2</sub>HPO<sub>4</sub>)
- Visicol (60 g Na<sub>2</sub>HPO<sub>4</sub>) (2000)
- OsmoPrep (48g Na<sub>2</sub>HPO<sub>4</sub>) (2005)

## Polyethylene Glycol Preps (PEG 3350 +E)

- GoLYTELY (4L) (1984)
- Colyte (4L) (1984)
- OCL Solution (4L) (1986)
- NuLYTELY (4L) (1991)
- Moviprep (2L) (2006)



# Bowel Prep Electrolyte Content (per recommended dosing)

	KCl	NaCl	NaHCO <sub>3</sub>	Na <sub>2</sub> SO <sub>4</sub>	Na <sub>2</sub> HPO <sub>4</sub>
GoLyteLy	x	x	x	X (23 g)	
Colyte	x	x	x	X (23 g)	
NuLyteLy	x	x	x		
Moviprep *		x		X (15 g)	
Visicol					X (60 g)
OsmoPrep					X (48 g)
Fleets					X (59 g)

\*sodium ascorbate, ascorbic acid, aspartame



## Controlled Phase 2/3 Trials Submitted for Bowel Preparation NDAs

Drug	# of Trials	# pts on study drug	Comparators
GoLYTELY	2	41	Combination of Magnesium sulfate or citrate, oral visacodyl + tap water enema in both trials
NuLYTELY	2	74	GoLYTELY
Fleets OSPS (59 g)	2	217	OSOPs (59 g) and GoLYTELY NuLYTELY and GoLYTELY
Visicol	3	458	Visicol 42 and 24 g NuLYTELY NuLYTELY



## Exclusion Criteria:

GoLYTELY	Not available
NuLYTELY	Not available
Fleets OSPS (59 g)	Know or suspected renal insufficiency; or dehydration or pre-existing electrolyte disturbance
Visicol	Acute or chronic renal insufficiency (creatinine > 2.0 mg/dL); or electrolyte imbalance including hyponatremia, hypocalcaemia, or hyperphosphatemia



# Safety Assessment

Drug	Safety Assessment	Deficiency
GoLYTELY	Labs on screening & colonoscopy days	No Cr, Ca, Mg blood levels, no evaluations after colonoscopy; labs taken right after study drug administered; no TQT study
NuLYTELY	Labs on screening & colonoscopy days	No labs or physical exam after colonoscopy; no TQT study
Fleets OSPS (59 g)	Labs on screening & colonoscopy, & 1 day after colonoscopy	Last labs and follow-up exam performed 1 day after colonoscopy; no post dose ECGs or physical exam; no TQT study
Visicol	Labs + ECG on screening, colonoscopy, + 2 or 3 days after colonoscopy	Last labs + follow-up exam performed 3 days after colonoscopy; not TQT study



## Phosphate Abnormalities: Visicol Phase 3 Trials

	Phase 3 Trial	Visicol (60 mg) N=427	NuLYTELY N=432
Mean baseline phosphate level (mg/dL)	301	3.2	3.3
	302	3.3	3.4
Mean colonoscopy-day phosphate level (mg/dL)	301	6.9	3.3
	302	7.2	3.3
Hyper-phosphatemia on colonoscopy day (%)	301	96	1
	302	96	0
Hypo-phosphatemia 2-3 days after colonoscopy (%)	301	37	3
	302	37	3



## Phosphate Abnormalities: Visicol Phase 2 Trial

	Visicol (60 g) N=31	Visicol (42 g) N=34	Visicol (24 g) N=34
Mean baseline phosphate level (mg/dL)	3.2	3.2	3.2
Mean colonoscopy-day phosphate level (mg/dL)	6.9	6.6	6.0
Hyper-phosphatemia on colonoscopy day (%).	83	100	97

*Labs not performed post-colonoscopy day if nl on day of colonoscopy*



## Na, K, Ca Abnormalities on Colonoscopy-Day: Visicol Phase 3 Trials

	Study	Visicol (60 mg) N=427 %colonoscopy day (% 2-3 days later)	NuLYTELY N=432 %colonoscopy day (% 2-3 days later)
Hyponatremia	301	6 (27)	22 (36)
	302	9 (29)	22 (31)
Hypokalemia	301	26 (4)	3 (3)
	302	30 (7)	3 (1)
Hypocalcemia	301	47 (9)	12 (10)
	302	47 (15)	6 (8)



## Na, K, Ca Abnormalities on Colonoscopy-Day: Visicol Phase 2 Trials

	Visicol (60 g) N=31 %	Visicol (42 g) N=34 %	Visicol (24 g) N=34 %
Hyponatremia	7	12	3
Hypokalemia	26	12	9
Hypocalcemia	47	52	44



# Electrolyte Abnormalities: Fleet OSPS Trial (PS9902)

	90 mL OSPS (59 g) n=74 %	60mL OSPS (40 g) n=75 %	GoLYTELY N=73 %
Hyperphosphatemia <sup>1</sup>	95	89	0
Hypophosphatemia <sup>2</sup>	28	32	13
Hypokalemia	20	27	3
Hyponatremia	1	4	1
Hypernatremia	6	0	0
Hypocalcemia	8	9	3
Hypomagnisemia	10	5	2

*All labs day of procedure except phosphate levels are day of coloscopy<sup>1</sup> and 24 hrs post<sup>2</sup>*



## SAEs due to Electrolyte Abnormalities (Seizures, Arrhythmias, & ARF) In controlled Trials

Brand	Treatment Groups	Total # of patients on study drug in controlled trials	SAEs probably or possibly drug-related
GoLYTELY	GoLYTELY	31	None
	Combination*	24	None
Fleet OSPS (60 g)	OSPS (59 g)	217	None
	OSPS (40 g)	75	None
	GoLYTELY	211	None
	NuLYTELY	141	None
NuLYTELY	NuLYTELY	74	None
	GoLYTELY	78	None
VISICOL (60 g)	Visicol (60 g)	458	1 case of Atrial Fib
	NuLYTELY	432	None
	Visicol (42 g)	33	None
	Visicol (24 g)	34	None

\*Combination included Magnesium citrate or sulfate, bisacodyl, and enema



## Summary from Clinical Trials

- Large % patients taking Sodium Phosphate products had hyperphosphatemia compared to PEG-based products
  - Many of these patients developed hypokalemia and hypocalcemia
- Many patients who took either developed hyponatremia
- Bowel prep trials lacked optimal safety follow up labs and excluded patients at higher risk of electrolyte abnormalities
- No significant SAEs due to electrolyte abnormalities in the PEG and Sodium phosphate based RX and OTC bowel preps trials



# OSE - Post-Market Safety Review: AERS Database

- Sodium phosphate oral solution (SPOS)
- Sodium phosphate tablet (SPT)
- Polyethylene glycol (PEG)

# Sodium phosphate oral solution (SPOS)

- Acute Renal Failure (n=33)
  - onset 1-2 days up to approx. 2 months
- Seizure (n=2)
  - 2 died (93 yo female developed severe/ARF; seizure/aspiration pneumonitis)
  - Both patients were given doses of SPOS > 90 mL
- Serious Cardiac Events (n=12)
  - Cardiac arrest (7 (5 fatal)), QT prolongation (5)
  - At least 6 patients given SPOS doses > 90 mL
  - History of CRF (1), history of nephrectomy (1), history of nephrostomy (1)
  - Most pts had electrolyte abnormalities
  - Many cases were older and provided little information

# Sodium phosphate tablet (SPT)

- Acute Renal Failure (n=11)
  - Onset 1-2 days up to 2 months
- Seizure (n=10)
  - Hyponatremia (10), hypokalemia (8), hyperkalemia (1), hypocalcemia (7), normocalcemic (2)
  - Onset 2-16 hours after starting prep
  - Medical History: Hyperparathyroidism (1), hyponatremia (1)
  - 9 had not history of seizure
  - Concomitant medication: Nortriptyline (1)

# Sodium phosphate tablet (SPT) (cont'd)

- Seizure patients
  - Doses used: Pt took 28 SPT as a single dose (1), pt took 28 SPT (20 and 8 tablets) only 4 hours apart (1); 2 patients were suspected to have used excess fluid.
- Serious cardiac events (n=2)
  - 1 died from bronchial asthma, patient with hx of cardiac arrhythmia on quinidine
  - QTc prolongation (43 yo female with underlying IBD) found to have decreased calcium, potassium and magnesium and increased phosphate levels.

# Polyethylene glycol (PEG)

- Acute renal failure (ARF) (n=1)
  - patient with end stage liver disease, taking furosemide
- Seizure (n=5)
  - All patients hyponatremic (Na =111-122)
  - 4/5 females
  - 1 death from seizure/cardiac arrest (history of DM and ESRD, taking diuretic)
- Serious cardiac events (n=1)
  - Patient (86 yo female) developed ventricular fibrillation with K=2.7



# Oral Sodium Phosphate Bowel Preps Safety Issue:

## Acute Phosphate Nephropathy

# Acute Phosphate Nephropathy

## Definition:

### **A form of acute kidney injury**

- associated with deposits of calcium-phosphate crystals in the renal tubules**
- may result in permanent renal function impairment.**
- Acute phosphate nephropathy is a rare, serious adverse event that has been associated with the use of OSPs**



# Acute Phosphate Nephropathy

- *Information for Healthcare Professionals* sheet and an *FDA Science Paper* issued 2006
- Information incorporated into Rx labeling
- FDAAA letter requiring Class Labeling Changes, Communication Plan and a Med Guide (2008)
- 2 Citizen Petitions:
  - FDA agreed to increase warnings on the prescription products
  - FDA agreed that OTC sodium phosphate bowel preps should be removed from marketing.
    - These oral sodium phosphate laxatives remain on the market



# Required Box Warning

## – **WARNINGS**

- There have been rare, but serious reports of acute phosphate nephropathy in patients who received oral sodium phosphate products for colon cleansing prior to colonoscopy.
  - Some cases have resulted in permanent impairment of renal function and some patients required long-term dialysis.
  - While some cases have occurred in patients without identifiable risk factors, patients at increased risk of acute phosphate nephropathy may include those with increased age, hypovolemia, increased bowel transit time (such as bowel obstruction), active colitis, or baseline kidney disease, and those using medicines that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]). See **WARNINGS**.
- It is important to use the dose and dosing regimen recommended (pm/am split dose). See **DOSAGE and ADMINISTRATION**.



# Warnings and Precautions

- **Renal Disease, Acute Phosphate Nephropathy, and Electrolyte Disorders**
  - There have been rare, but serious, reports of renal failure, acute phosphate nephropathy, and nephrocalcinosis in patients who received oral sodium phosphate products (including oral sodium phosphate solutions and tablets) for colon cleansing prior to colonoscopy. These cases often resulted in permanent impairment of renal function and several patients required long-term dialysis. The time to onset is typically within days; however, in some cases, the diagnosis of these events has been delayed up to several months after the ingestion of these products. Patients at increased risk of acute phosphate nephropathy may include patients with the following: hypovolemia, baseline kidney disease, increased age, and patients using medicines that affect renal perfusion or function [such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs)].
  - Use OsmoPrep with caution in patients with impaired renal function, patients with a history of acute phosphate nephropathy, known or suspected electrolyte disturbances (such as dehydration), or people taking concomitant medications that may affect electrolyte levels (such as diuretics). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have their electrolytes corrected before treatment with OsmoPrep Tablets.



## **When prescribing OSPs for bowel preparation, healthcare professionals should consider the following points:**

- Provide easy to understand instructions to the patient about how to prepare for the procedure, and tell them what symptoms to be aware of in order to help them recognize, and possibly mitigate the risk of acute kidney injury.
- Instruct patients of the need to drink sufficient quantities of clear fluids before, during and after bowel cleansing. There are publications suggesting that use of an electrolyte or carbohydrate-electrolyte replacement solution may help decrease the electrolyte abnormalities and hypovolemia associated with OSP bowel cleansing.
- Avoid exceeding the maximum recommended OSP doses.
- Avoid concomitant use of laxatives containing sodium phosphate.
- Avoid use of OSPs in children under 18 years of age.
- Use OSPs with caution in patients over 55 years of age.
- Use OSPs with caution in patients with dehydration, kidney disease, delayed bowel emptying, or acute colitis.
- Use OSPs with caution in patients taking medicines that affect kidney function or perfusion, such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and possibly non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients who may be at increased risk for acute phosphate nephropathy, including those with vomiting and/or signs of dehydration, obtain baseline and post-procedure labs (electrolytes, calcium, phosphate, BUN and creatinine). For smaller, frail individuals, also monitor glomerular filtration rate.
- Consider hospitalization and intravenous hydration during bowel cleansing to support frail patients who may be unable to drink an appropriate volume of fluid or who may be without assistance at home.



# PMR for Oral Sodium Phosphate (Visocol and Osmoprep)

- Protocol should include an appropriate pre-specified primary outcome to assess acute kidney injury (e.g., increase in baseline creatinine following treatment).
- Laboratory testing at baseline and at pre-determined intervals following bowel cleansing should be assessed.
- Overall duration of follow-up should be specified, and your rationale for the adequacy of such follow-up should be submitted

# Literature

Brunelli et al reported on a case control study in a cohort of patients with BL serum CR  $\leq 1.5$  mg/dL who underwent outpatient colonoscopy.

- Defined kidney injury as a rise in serum CR  $> 0.5$  mg/dL and/or 25% between values obtained during 6 months pre and post procedure
- Concluded: “exposure to phosphosoda was not more common among patients with incident kidney injury (adjusted OR 0.70; 95% IC 0.44 -11.1), and sensitivity analyses that considered other definitions of kidney injury did not suggest a different conclusion.



# Literature

- Hurst et al studied 9799 patients undergoing colonoscopy
  - Acute kidney injury we defined as  $> 50\%$  increase in baseline serum creatinine,
  - 114 cases were indentified; 1.29% in the OSP group and 0.92% in the PEG group.
  - Univariate analysis did not find any difference between the two
  - Multivariate analysis demonstrated that OSPs were associated with increase risk of AKI of OR 2.35; 95% CI 1.51. to 3.66).



# NDA 22-372

## SuPrep<sup>®</sup> Bowel Prep Kit Braintree Laboratories, Inc.

Tamal Chakraborti, Ph.D.  
Pharmacologist

Division of Gastroenterology Products



## Indication and Dosage

- **Indication:** For cleansing of the colon as a preparation for colonoscopy in adults
- **Dosage:** Two 6 oz bottles
  - Sodium sulfate: 35.02 g
  - Potassium sulfate: 6.26 g
  - Magnesium sulfate: 3.20 g



# Mechanism of Action

- The pharmacodynamic action of Suprep relies on the retention of water in the intestines
- The principal osmotic components of Suprep are magnesium and sulfate, with sulfate contributing the larger proportion of osmotic load
- Both ions are poorly absorbed above a point of saturation, forcing water to remain in the intestines



# Toxicology Studies

- Rat (Oral, 28-Day)
- Dog (Oral, 28-Day)



# Rat

<b>Group</b>	<b>Test Article</b>	<b>Dose (g/kg/day)</b>	<b>Dose Volume (mL/kg)</b>
<b>1</b>	Vehicle	0	15
<b>2</b>	SuPrep	1.25	15
<b>3</b>	SuPrep	2.5	15
<b>4</b>	SuPrep	5.0	15
<b>5</b>	OSP (Fleet <sup>®</sup> )	5.13	15



# Mortality

<b>SEX</b>	<b>MALES (N = 10)</b>					<b>FEMALES (N = 10)</b>				
<b>GROUP</b>	<b>SUPREP</b>				<b>OSP</b>	<b>SUPREP</b>				<b>OS P</b>
<b>Dose (g/kg/day)</b>	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
<b>No. of Deaths</b>	0	0	0	0	8	0	0	0	0	7



# Serum Chemistry (Day 28)

SEX	MALES					FEMALES				
	SUPREP				OSP	SUPREP				OSP
GROUP	SUPREP				OSP	SUPREP				OSP
Dose (g/kg/day)	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Chloride	103	100**	97**	95**	96	103	100**	97**	94**	94**
Potassium	4.7	4.5	4.0**	3.6**	3.7*	4.4	4.3	3.9**	3.6**	3.5**
Sodium	144	144	143	142	147	144	143	141**	140**	142
Bicarbonate	25	26	29**	30**	24	21	22	23	24	27**
Calcium	11.1	11.1	11.2	11.3	7.2	11.1	11.0	10.9	11.1	9.9**
Phosphorus	8.5	8.8	8.1	8.1	23.5**	7.5	7.6	7.2	7.8	8.9*
Calc. Serum Osmolality	300.4	298.8	297.2	297.3	310.6	306.6	291.6**	295.2**	292.3**	296.1
Creatinine	0.2	0.2	0.1	0.1	0.7	0.3	0.3	0.2	0.2	0.3

\* = p<0.05; \*\* = p<0.01



# Urine Chemistry (Day 28)

SEX	MALES					FEMALES				
GROUP	SUPREP				OSP	SUPREP				OSP
Dose (g/kg/day)	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Sodium	27	201**	409**	390**	289	55	218	370**	398**	301**
Potassium	105	128	175*	129	53	110	166	186*	183*	78
pH	6.8	6.1	6.9	8.0**	6.3	6.6	6.2	6.5	7.9**	6.5
Creatinine	75.7	83.7	59.0	25.6**	16.9*	65.3	89.4	53.2	23.4**	22.3*

\* = p<0.05; \*\* = p<0.01



# Renal Function Values (Day 28)

MALES						FEMALES				
SUPREP					OSP	SUPREP				OSP
Dose (g/kg/day)	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
CCR	14.8	13.7	10.3	11.6	2.27	6.7	7.03	6.45	3.19**	4.51
SCR	0.005	0.03	0.06**	0.14**	0.18	0.01	0.03	0.07**	0.09**	0.12**
FSE	0.04	0.25	0.64**	1.56**	7.61	0.16	0.47	1.24**	2.80**	2.52**
PCR	0.61	0.64	0.94	1.79**	1.22*	0.66	0.77	1.33*	1.48**	1.26

CCR = Creatinine Clearance Rate; SCR = Sodium Clearance Rate; FSE = Fractional Sodium Excretion ; PCR = Potassium Clearance Rate; \* = p<0.05; \*\* = p<0.01



# Histopathology (Day 28)

SEX	MALES (N = 10)					FEMALES (N= 10)				
GROUP	SUPREP				OSP	SUPREP				OSP
DOSE (g/kg/day)	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Adrenal Cortex: Vacuolation	0	2	5	6	4	0	0	0	6	2
Colon: Dilatation, Lumen	1	4	4	7	3	1	3	5	6	5
Jejunum: Dilatation, Lumen	0	2	4	6	3	0	0	1	0	1



# Histopathology (Contd.)

SEX	MALES (N = 10)					FEMALES (N = 10)				
GROUP	SUPREP				OSP	SUPREP				OSP
DOSE (g/kg/day)	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Kidney: Tubular degeneration	0	0	0	0	10	0	0	0	0	10
Kidney: Mineralization	0	0	0	0	10	1	0	1	1	10
Stomach: Mineralization	0	0	0	0	8	0	0	0	0	8
Heart: Myocardial degeneration	0	0	0	0	7	0	0	0	0	9
Aorta: Mineralization	0	0	0	0	2	0	0	0	0	1

# Summary (Rat)

## SuPrep

- Mortality: None
- Organ Toxicity
  - Adrenal cortex: Minimal-mild vacuolation
  - Colon/Jejunum: Dilated lumen
  - Possibly the kidney

## Sodium Phosphate

- Mortality: 75% (renal insufficiency)
- Organ Toxicity
  - Kidney: Tubular degeneration and mineral deposition (calcium phosphate)
  - Stomach: Mineralization
  - Heart: Myocardial degeneration
  - Aorta: Mineralization



# Dog

<b>Group</b>	<b>Test Article</b>	<b>Dose (g/kg/day)</b>	<b>Dose Volume (mL/kg)</b>
<b>1</b>	Vehicle	0	15
<b>2</b>	SuPrep	1.25	15
<b>3</b>	SuPrep	2.5	15
<b>4</b>	SuPrep	5.0	15



# Results

- **Clinical Signs:** Emesis, excessive salivation, white frothy material around the mouth, excessive drinking of water and soft and/or mucoid feces and/or diarrhea
- **Urinalysis:** Increased urine pH and increased sodium excretion
- **Histopathology:** No significant findings



# Conclusions

- SuPrep caused electrolyte imbalance and metabolic alkalosis
- OSP caused organ toxicity in the kidney (renal tubular degeneration and mineral deposition) and the heart (myocardial degeneration)



# SuPrep Bowel Prep Kit NDA 22-372

**Jane P. F. Bai, Ph.D**  
**Sue-Chih Lee, Ph.D. (Team Leader)**  
**Division III**  
**Office of Clinical Pharmacology**



## **Sponsor's rationale for developing sulfate into a product**

- According to the sponsor, the amount of phosphate absorbed and the extent of hyperphosphatemia appear to contribute to precipitation of calcium phosphate crystals in the kidney, causing “acute phosphate nephropathy”. “Sulfate salts are generally more poorly absorbed than phosphates.”



# Study BLI800-202: pharmacokinetic study

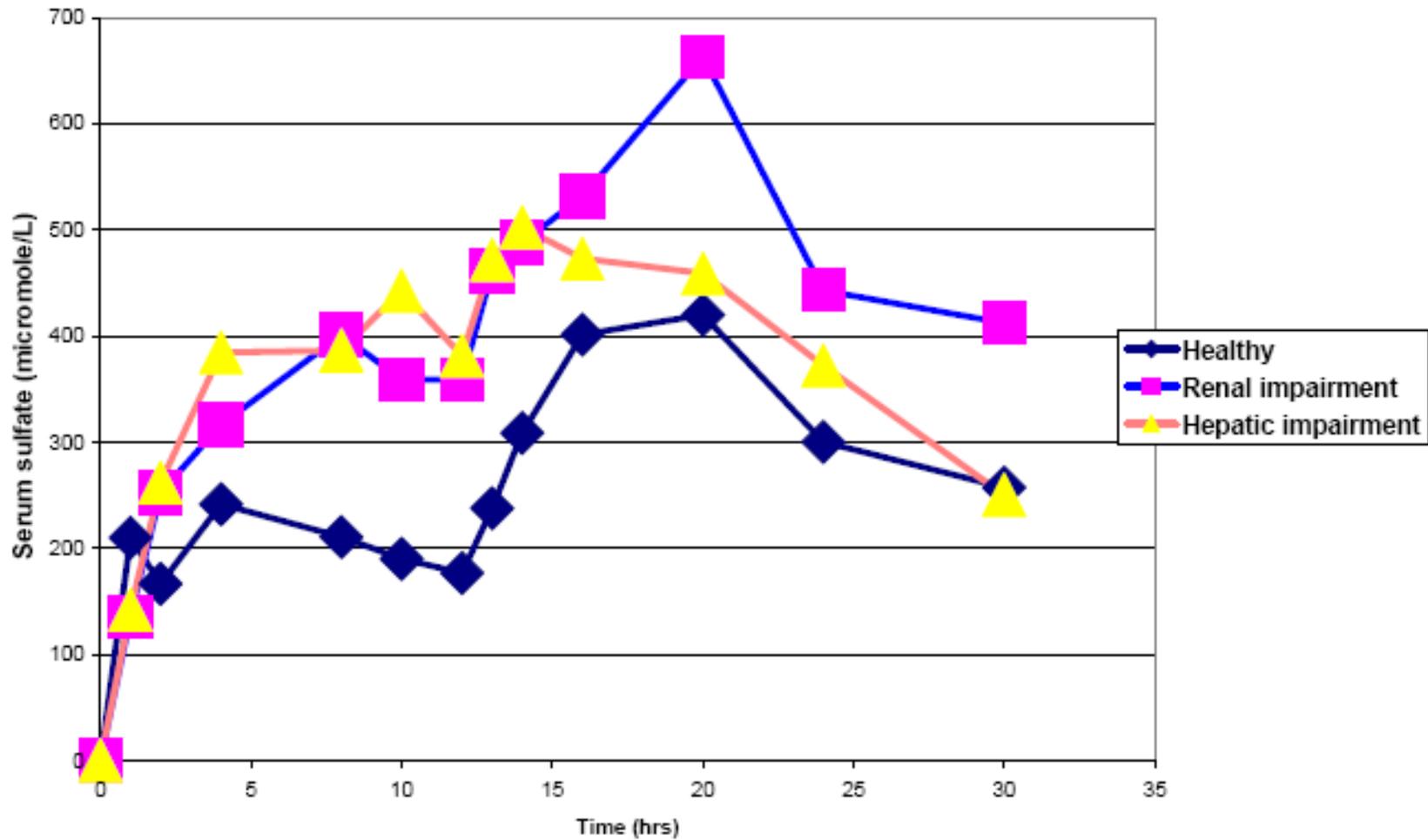
- **A single center, open label, safety and pharmacokinetic (PK) study of the effects of administering BLI800 to patients with mild-moderate hepatic impairment or moderate renal disease and healthy matched controls. To-be-marketed formulation.**
- **N=6 for each group; Age: healthy, 51.2 (5.74); renal impairment, 53.8 (7.96); hepatic impairment, 49.0 (6.93)**
- **Hepatic impairment: five patients with Class A Child- Pugh scores (5-6 points) and one with Class B Child-Pugh scores (8 points)**
- **Renal impairment: GFRs (42-48 ml/min) (MDRD equation)**
- **Serum chemistry, ECG**



# Dosing schedule

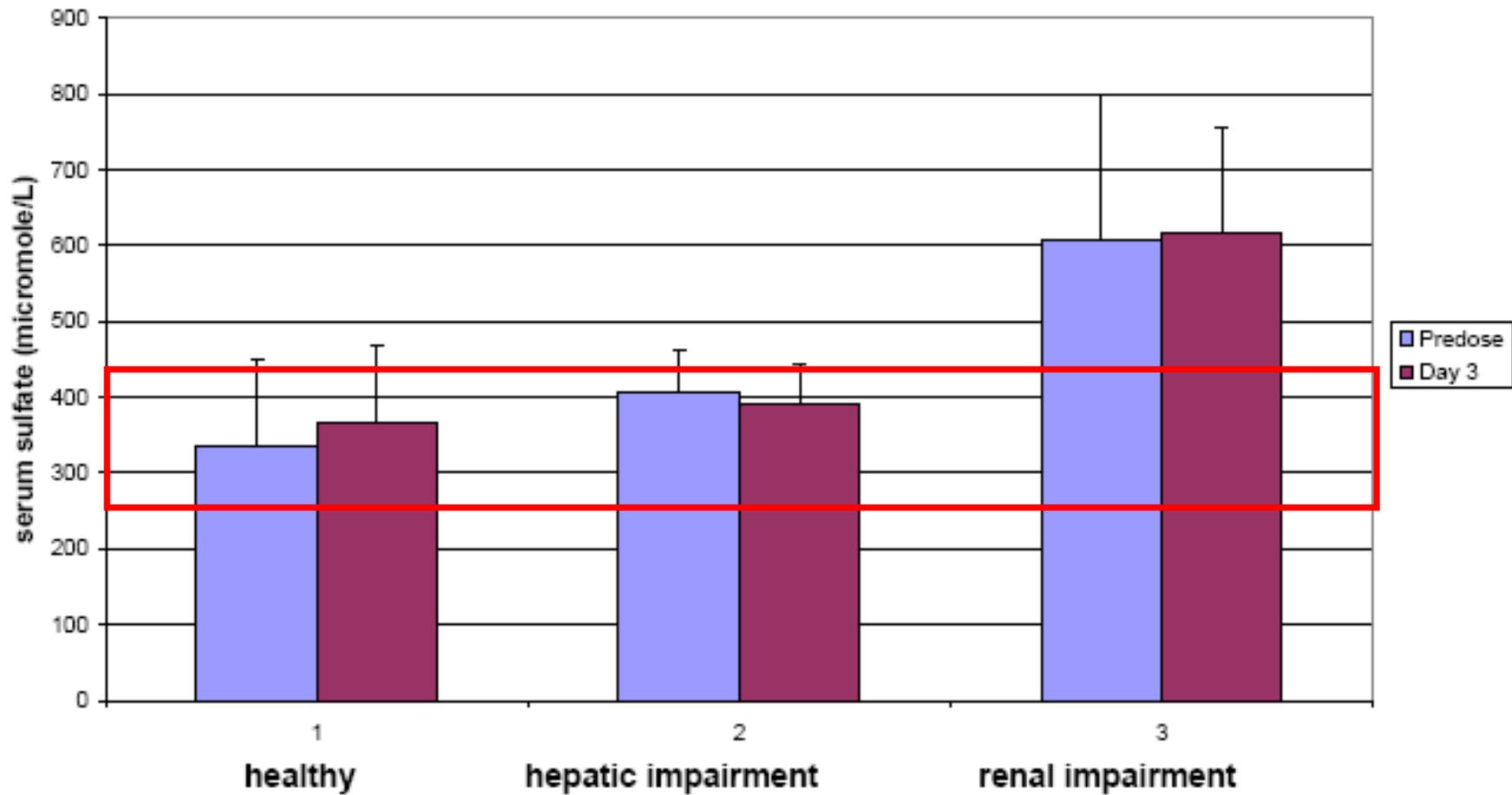
- **BLI800 was administered in two 6-ounce half doses separated by 12 hours.**
- **6 AM Day 1 Drug Administration: The contents of the 6-ounce bottle of BLI800 (half dose 1) was poured into a mixing cup and then the cup was filled with water to the 16 ounce fill line. Beginning at 6 AM, the patients drank the entire 16-ounce volume over the next 15 minutes, followed by two additional 16-ounce glasses of water over the next 1-3 hours. Additional amounts of water or clear liquids were allowed at any time and in any amounts.**
- **6 PM Day 1 Drug Administration: The second half of the BLI800 dose was administered to the patients at 6 PM as described above.**

**Baseline-corrected serum sulfate concentration/time profiles**





## Return of serum sulfate to predose levels





## **Any difference in serum electrolytes following Suprep**

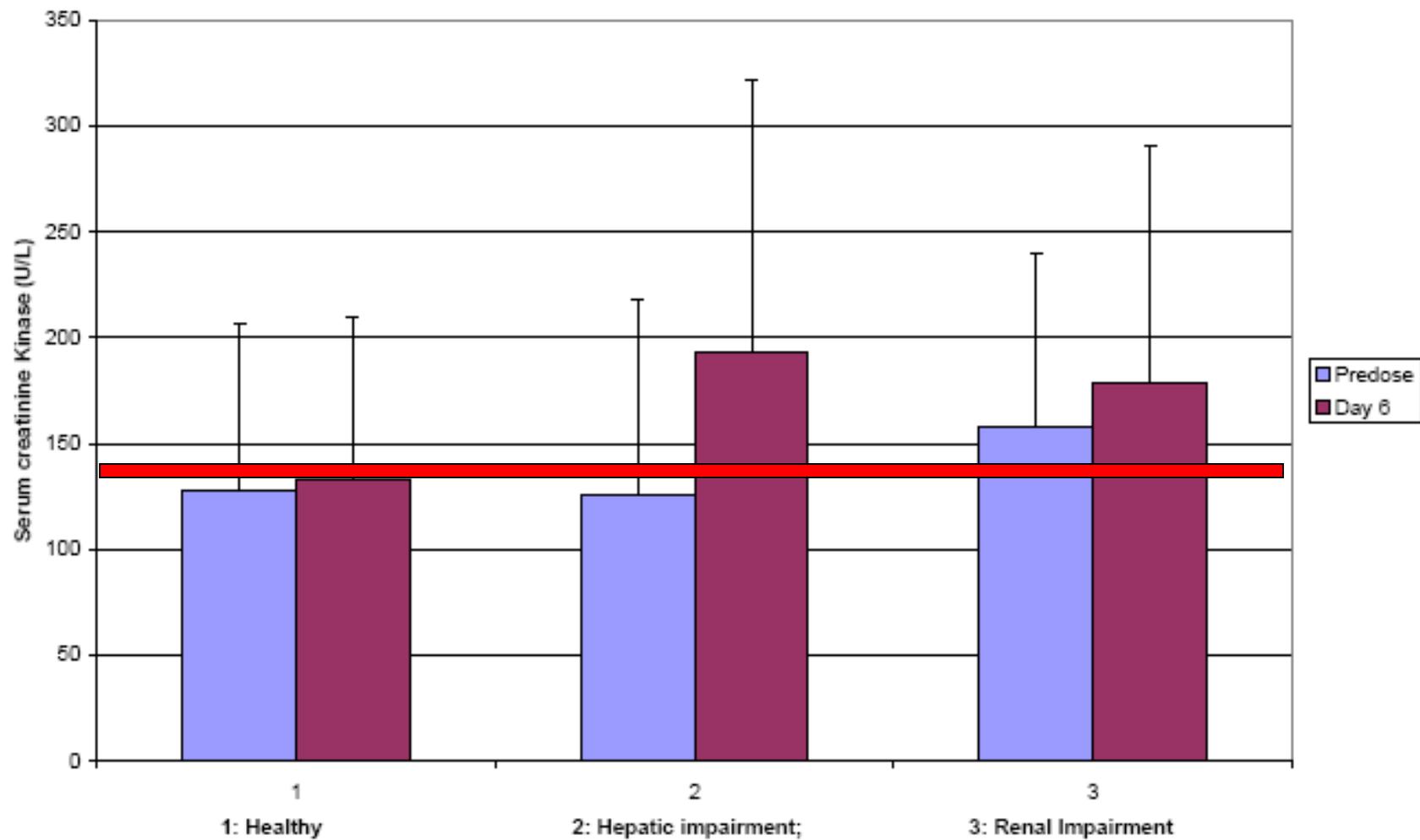
- No treatment-emergent differences between either of the two patient groups and the healthy volunteers with regard to sodium, potassium, and magnesium in the serum.

# Serum creatinine levels

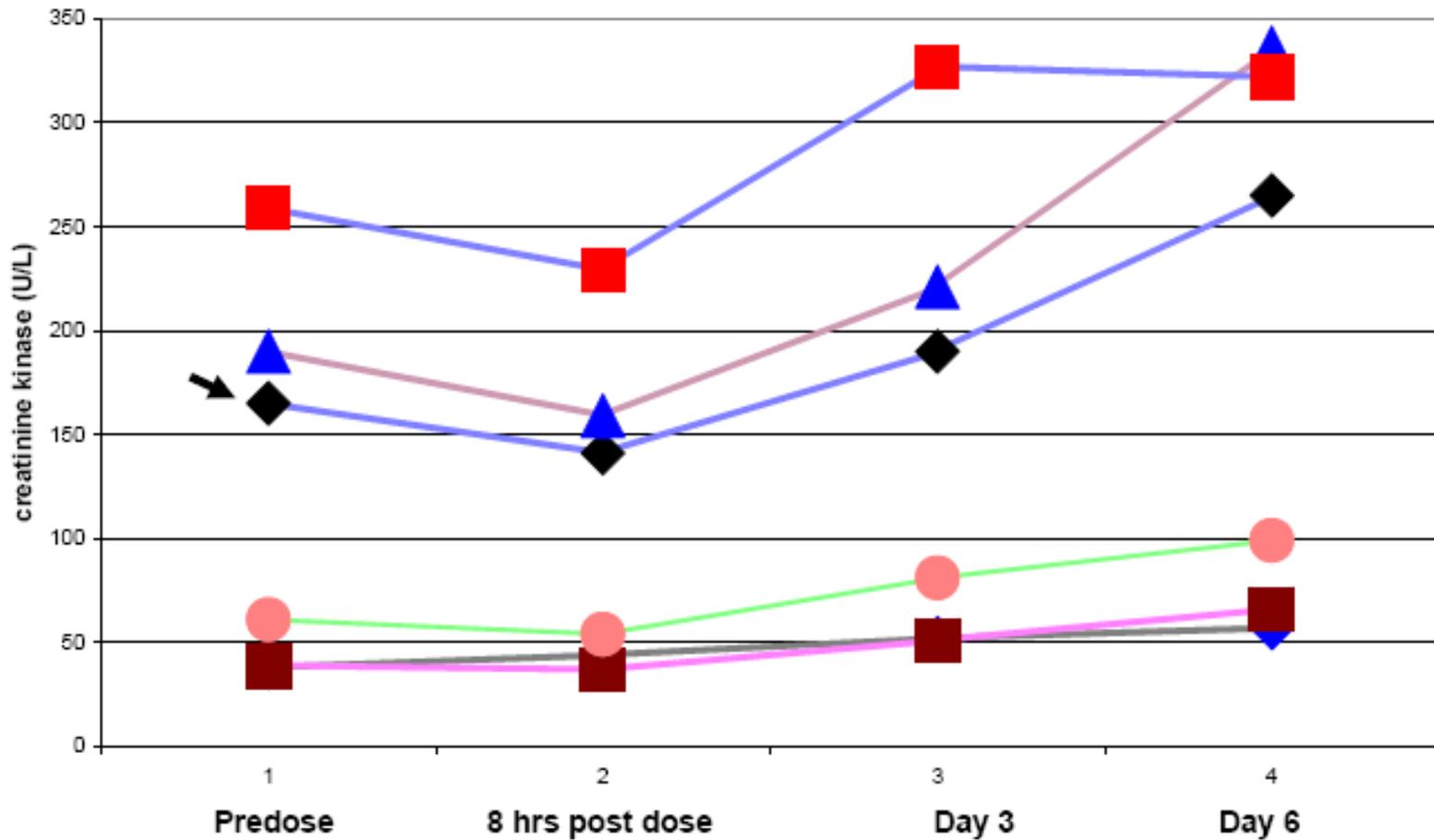
- Serum creatinine levels were within the normal range in the healthy and hepatic impairment groups throughout the study.
- Respective mean (SD) serum creatinine levels at predose and on day 6 in renal impairment group were 1.73 (0.34) mg/dL and 1.82 (0.55) mg/dL



## Comparison of creatine kinase levels



### Serum creatine kinase levels (hepatic impairment)



# Serum calcium

In all 18 subjects, serum calcium showed a trend of gradual decreasing after split dose 1 and 2, and then increasing back to individual predose levels. The subjects with low serum calcium are listed below.

- 004: 8.5mg/dL at 12hrs post split dose 2
- 009: 8.4 mg/dL at 8hrs post split dose 2
- 016: <8.5mg/dL from 2 hrs post split dose 1 to Day 3 and was even lower (7.8 mg/dL) at 8 hrs post split dose 2
- 018: 8.3mg/dL at 8 hrs post split dose 2

Bradycardia and abnormal ECG: transient, not sustained.

- 004, 005, 009

Note: normal serum calcium in adults, 8.5-10.5 mg/dL



# Summary

- Serum sulfate levels returned to predose values by day 3 in all three groups.
- Serum creatinine levels were normal in healthy and hepatic impairment groups throughout the study. Renal impairment group showed no difference between day 3 and predose value.
- Serum creatine kinase levels were higher than normal on day 6 in hepatic impairment, and from predose to day 6 in renal impairment.

# Suggestions: Safety issue

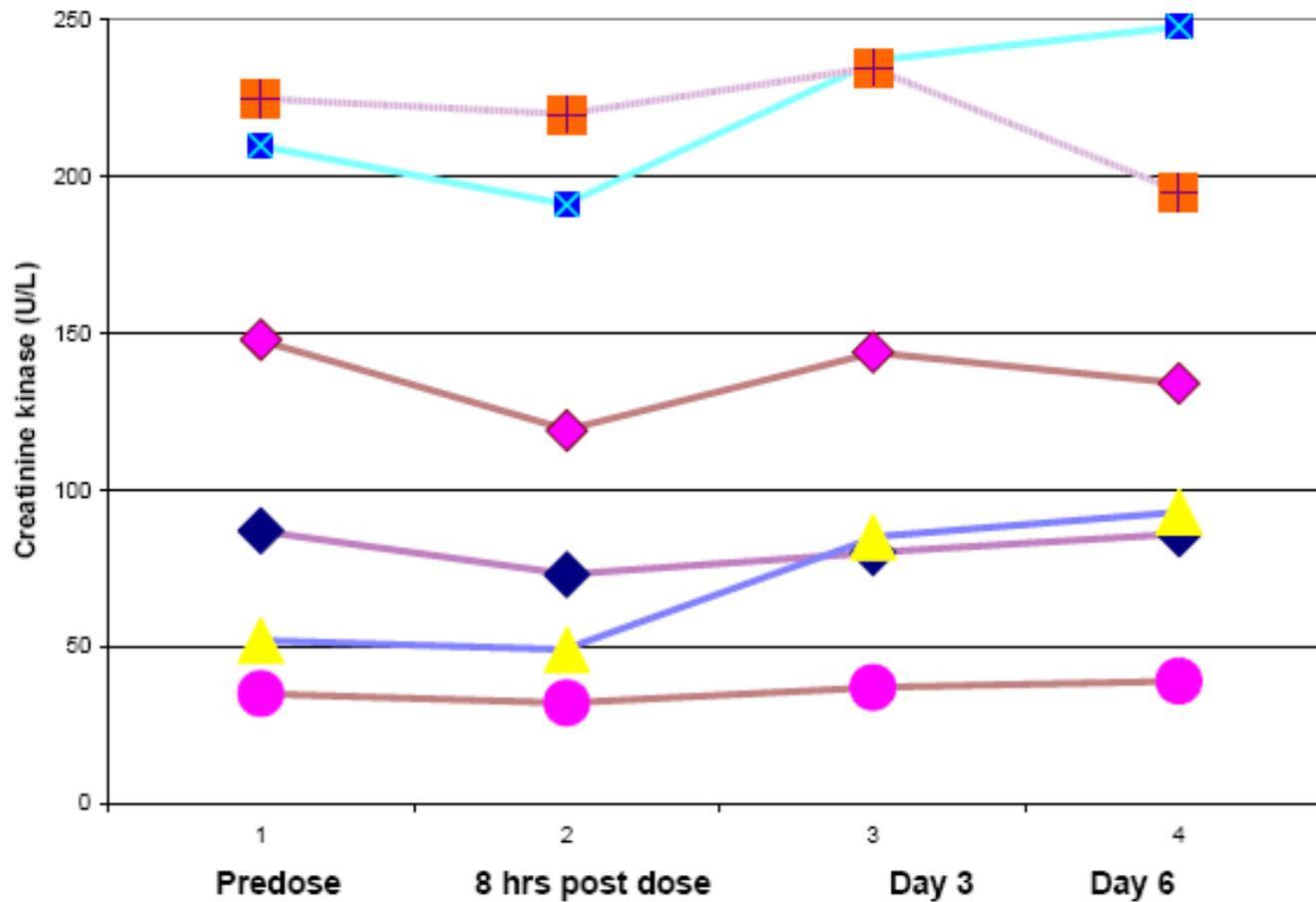
- Post-marketing commitment
  - A clinical study with extensive serum chemistry up to 4 weeks
    - Intense monitoring of CK (including CKMB), ECG, and calcium up to 4 weeks (days 1 & 2, weeks 1 & 2)
    - Population PK/PD analysis: exposure/response relationship where responses include markers in serum chemistry and CK.
      - Covariates: age, gender, hepatic functions (Child class A to B)



APPEARS THIS WAY ON ORIGINAL



### Serum creatinine kinase levels (Healthy subjects)





# Is calcium sulfate more soluble than calcium phosphate?

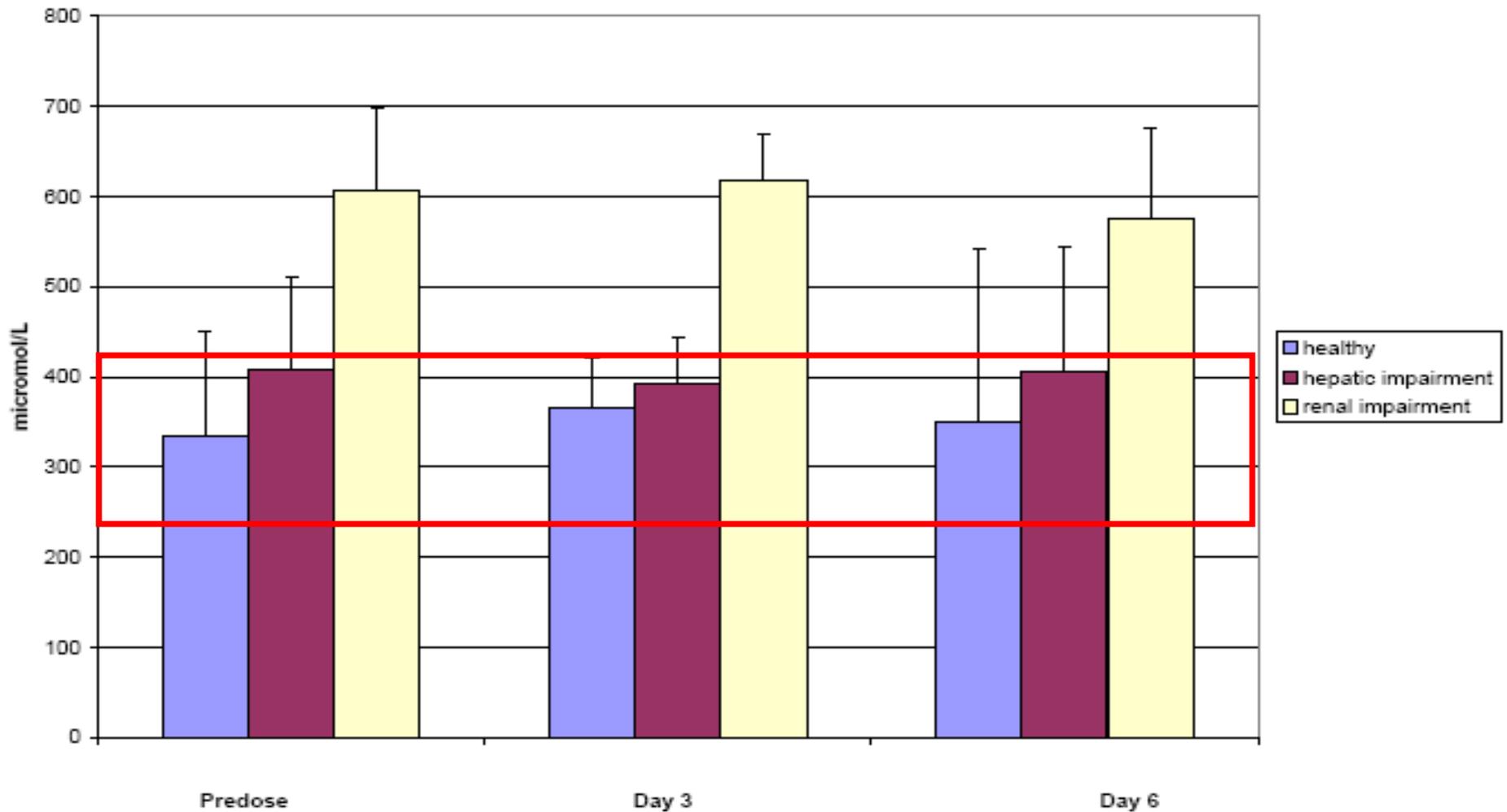
		Ksp
Calcium phosphate	$\text{Ca}_3(\text{PO}_4)_2$	$1 \times 10^{-26}$
Calcium sulfate	$\text{CaSO}_4$	$9.1 \times 10^{-6}$

California State University, Dominguez Hills

<http://www.csudh.edu/oliver/chemdata/data-ksp.htm>

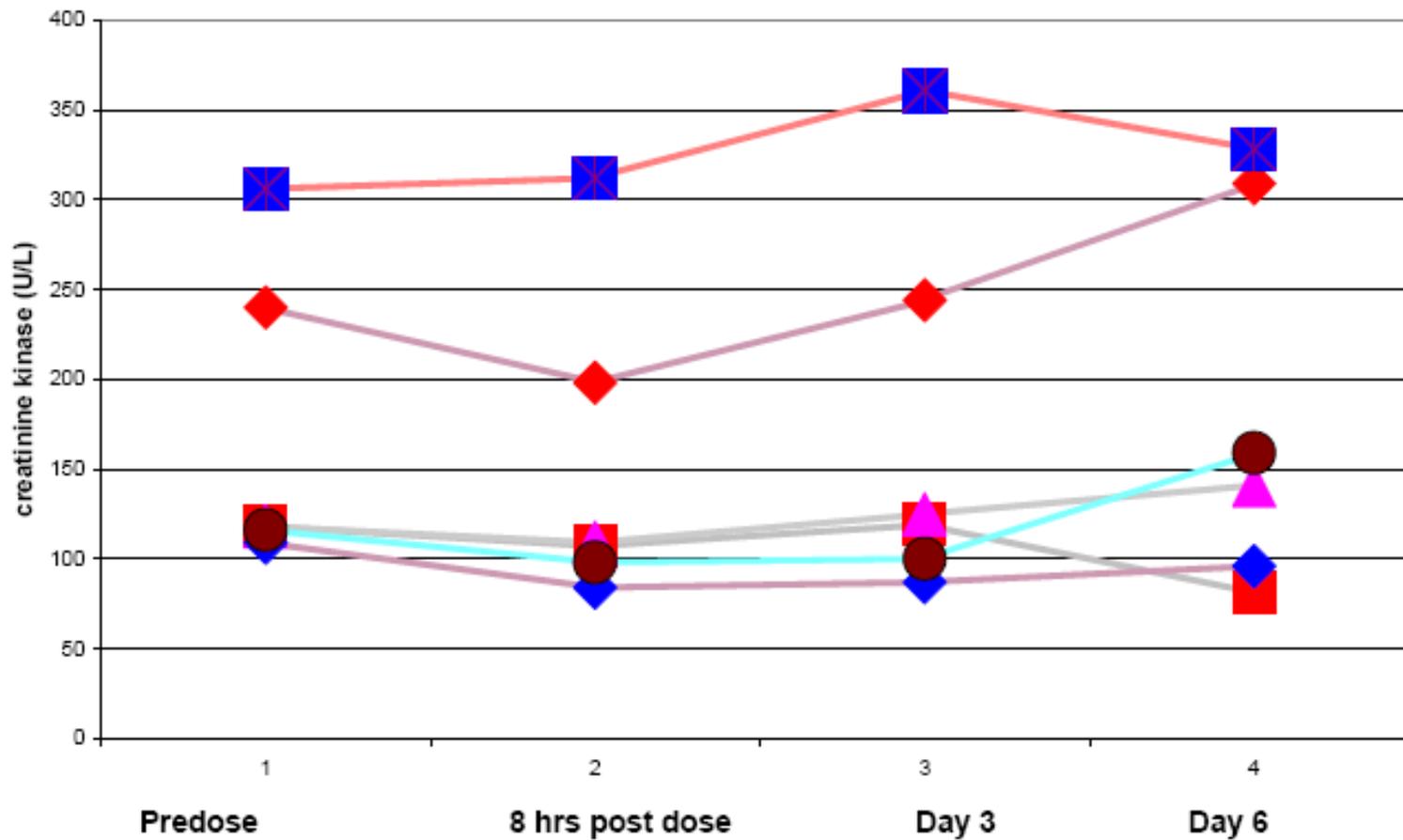


# Comparison of serum sulfate levels





### Serum creatinine kinase levels (renal impairment)





**NDA 22372**  
**SuPrep Bowel Prep Kit**  
**BLI800**  
**Braintree Laboratories, Inc.**

**Jasmine Gatti, M.D.**  
**Medical Reviewer**  
**Division of Gastroenterology Products**



# Presubmission Regulatory Activity

End-of-Phase 2 meeting summary:

- Do 4 week oral toxicity studies.
- Do PK studies in hepatic and renal patients
- Not do further non-clinical PK studies.
- Analyze geriatric and high risk patients (cardiac, vascular, diabetes) in Phase 3. Exclude seizure patients.
- Fleet's EZ-Prep and/or PEG-product was acceptable comparator change.
- No comment on adequacy N=360 (SuPrep safety database).
- FDA requested F/U at 1, 3, & 6 months (acute phosphate nephropathy in OSP \*).

\*Hurst F, *et al.* Association of oral sodium phosphate purgative use with acute kidney injury. *J AM Soc Nephrol* 18: 1-6; 2007.



# Presubmission Regulatory Activity

FDA response in Special Protocol Amendment:

- 30 day follow-up for SAE and labs acceptable.
- “the occurrence of acute nephrocalcinosis with the sulfate product is theoretical ... no significant change in urinary calcium... chemical tests of the saturation index for  $\text{CaSO}_4$  (the precipitant ...causing renal injury) showed that sulfate concentrations could be safely increased by a factor of 10 without approaching saturation.”



# Two Pivotal Studies: R, P , MC, SB, AC, Phase 3

## SuPrep vs. Moviprep

- **Moviprep (PEG+Electrolyte Product) 200 gm**  
Polyethylene glycol 3350, 15 gm Na<sup>+</sup> sulfate, 5.4 gm NaCl, 2.0 gm KCL, 9.4 gm ascorbate, 11.8 gm Na<sup>+</sup> ascorbate.
- **Study 301: N=387, Same day dose regimen.**
- **Study 302: N=364, Split day dose regimen.**



# Primary Efficacy Binary Outcome Results

(Received in IR 6/12/09)

Responder Success	Suprep %	Moviprep %
All Patients	85%	84%
Study 301	78%	76%
Study 302	92%	93%

# Diagnosis in Eligibility Criteria

## Inclusion Criteria

- routine screening
- cancer surveillance
- f/u barium enema results
- f/u endosonography
- f/u gastrointestinal bleed
- inflammatory bowel disease
- anemia of unknown etiology
- diarrhea or constipation of unknown etiology
- polypectomy
- laser therapy



# Safety Endpoints

Day of colonoscopy:

Symptom Questionnaire

- nausea, vomiting, bloating, cramping, discomfort
- rated as: 1- none; 2-mild; 3-bothersome, 4-distressing, and 5-severely distressing.



# Safety Assessments

## Day of colonoscopy

Symptom Questionnaires, Symptom Scale, VS, PE, AE's. Chemistry, hematology, and sulfate drawn post-dose prior to colonoscopy

## One month follow-up

- F/U labs, AE's only



## Total TEAE and Symptoms in Study 301 and 302

from response to IR 6/12/09

Percentages in (%)

Body System Preferred Term	BLI800 (n= 394)	MoviPrep (n=393)
# of patients	294 (75)	298 (76)
# of events	773	763
<b>CARDIAC Disorders</b>	1 (0.3)	2 (0.5)
AV Block	1 (0.3)	0
Bradycardia	0	1 (0.3)
Sinus Tachycardia	0	1 (0.3)
<b>GASTROINTESTINAL</b>	274 (70)	277 (71)
Abdominal Distension	188 (48)	205 (52)
Abdominal Pain	140 (36)	149 (38)
Anal Discomfort	1 (0.3)	2 (0.5)
Ischemic Colitis	0	1 (0.3)
Diarrhea	1 (0.3)	0
Dry Mouth	1 (0.3)	0
Large Intestine Perforation	0	1 (0.3)
Mouth Ulceration	1 (0.3)	0
Nausea	158 (40)	137 (35)
Vomiting	41 (10)	14 (4)



## Total TEAE and Symptoms in Study 301 and 302:

from response to IR 6/12/09.

Further details Slide 24 regarding Investigations

<b>INVESTIGATIONS</b>	3 (0.8)	0
ALT Increased	1 (0.3)	0
AST Increased	2 (0.5)	0
LDH Increased	1 (0.3)	0
CPK Increased	1 (0.3)	0
<b>RESPIRATORY</b>	0	1 (0.3)
Respiratory Distress	0	1 (0.3)
<b>RENAL and Urinary</b>	1 (0.3)	0
Dysuria	1 (0.3)	0
<b>GENERAL Disorders</b>	226 (57)	242 (62)
Chills	2 (0.5)	0
Discomfort	225 (57)	242 (62)
Feeling Hot	0	1 (0.3)
Non-cardiac chest pain	0	1 (0.3)
<b>NERVOUS SYSTEM</b>	6 (2)	5 (1)
Dizziness	0	1 (0.3)
Headache	6 (2)	4 (1)
<b>SKIN and Tissue</b>	1 (0.3)	0
Pruritis	1 (0.3)	0



# Major Deficiencies in Application

- Seven hundred serum sulfates frozen and sent to second lab, but, never analyzed (no amendment)
- Medwatch report submitted >1 year later: post-colonoscopy colonic perforation in MoviPrep patient
- Lack of pooled observer and patient outcome TEAE's. (22x increase in analysis: 43 to 773 events)



# Deaths and SAE

**SuPrep:** No serious AE's or deaths.

**MoviPrep:**

- 76 yo male (drug on 7/26/07 and 7/27/07), sustained respiratory and cardiac arrest, acute renal failure post-surgery. Expired

(b) (6)

- 52 yo male (drug on 8/2/07 and 8/3/07),

(b) (6)

for atypical chest pain.



## Other Significant AE

- **SuPrep** (same day regimen): 83 yo male had AVB prior to colonoscopy. D/C from the study. Possibly related to treatment.
- **MoviPrep** (split dose regimen): 52 yo female had focal mild ischemic colitis by biopsy. Resolved. Possibly related to treatment.



# Dropouts Due to AE's (all from same day dose)

from IR 10/28/08

## **SuPrep:**

- Moderate nausea
- Mild vomiting
- AV block (see prior slide)

## **MoviPrep:**

- Bloating and nausea



# Same Day versus Split Day Regimens: TEAE >1%

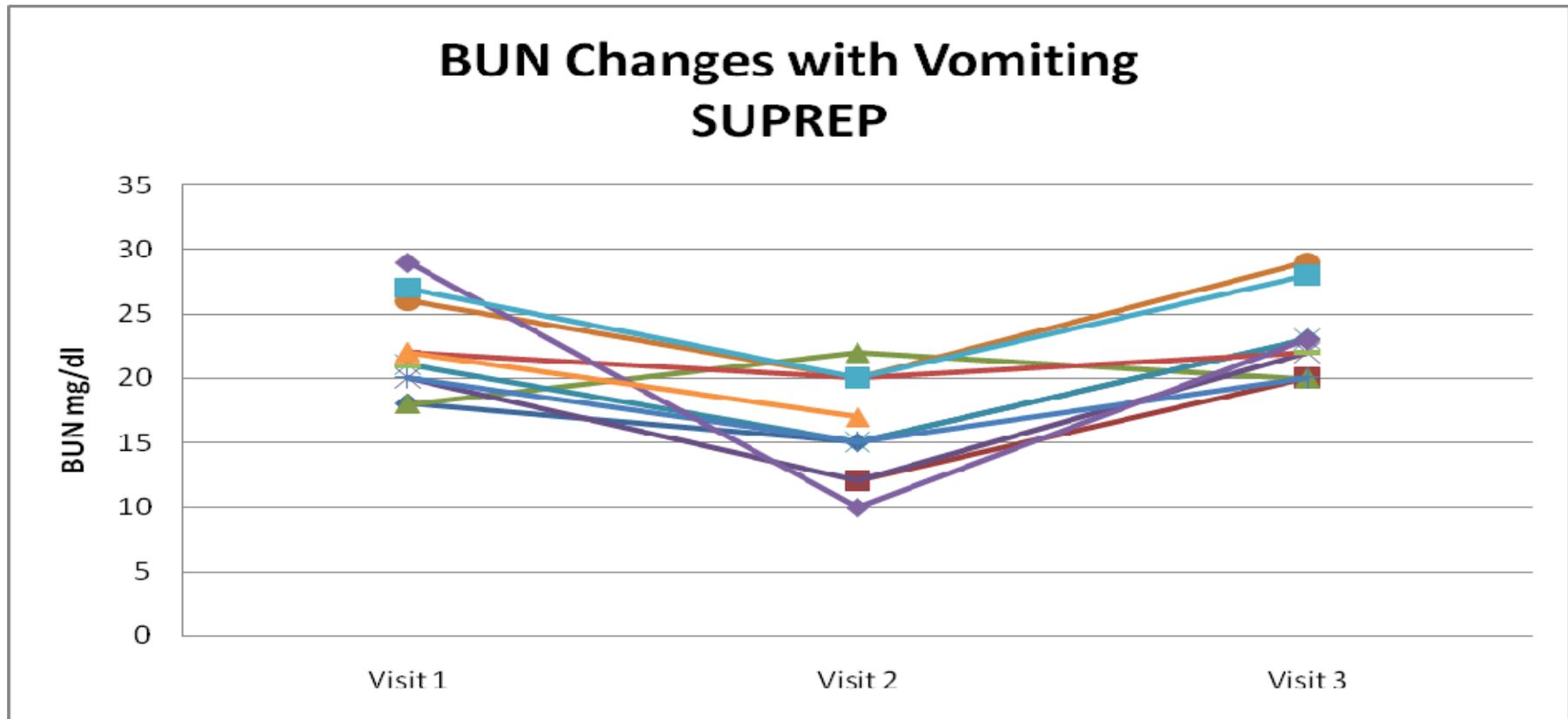
Symptom	Same (One) Day Regimen		Split Day Regimen	
	Suprep N=194	PEG-product N=193	Suprep N=181	PEG-product N=183
Discomfort	63%	60%	56 %	69%
Abdominal Distension	57%	55%	43%	54%
Abdominal Pain	37%	35%	38%	44%
Nausea	46%	39%	38%	34%
Vomiting	13%	4%	9%	4%
Headache	2 %	2%	1 %	1%

\* In both studies, Suprep patients were permitted to have a light breakfast followed by clear liquids and PEG-product patients were permitted to have a normal breakfast, light lunch, followed by clear liquids.



# SuPrep Bun Changes with Vomiting

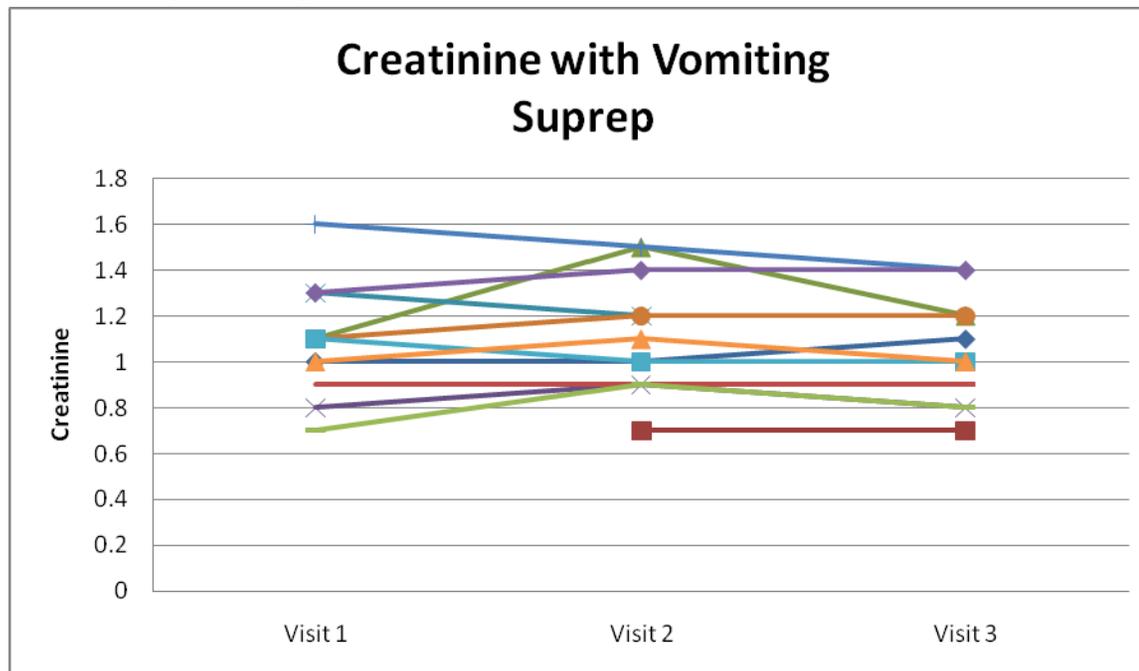
Visit 1=Screening; Visit 2=Day of colonoscopy; Visit 3=Follow-up at 30days  
BUN normal ( 6-19)





# SuPrep Creatinine With Vomiting

Visit 1=Screening; Visit 2=Day of colonoscopy; Visit 3=Follow-up at 30days  
Creatinine normal (.4-1.1)





# Bradycardia Contingency Tables

(no pulse taken on Visit 3)

Screening Pulse (BPM)	Suprep (N=375) Visit 2			Moviprep (N=376) Visit 2		
	<50 (n) (%)	<60 (n) (%)	Normal (n) (%)	<50 (n) (%)	<60 (n) (%)	Normal (n) (%)
<50	0	1 (0.3)	0	0	1 (0.3)	2 (0.5)
<60	0	10 (2.7)	18 (4.8)	4 (1.1)	18 (4.8)	15 (4.0)
normal	1 (0.3)	24 (6.4)	319 (85.1)	3 (0.8)	28 (7.4)	315 (83.8)



# CK Elevations (not in Total TEAE table) (Only 18021 had BUN/Creatinine and CK changes)

**Table 2: Patients in Phase 3 studies with post-treatment CK elevations >3 X ULN**

PT	TREATC	Screening visit CK, U/L	Visit 2 (colonoscopy) CK, U/L	Follow-up visit CK, U/L (post-treatment day)	Concomitant medications	Age (yrs)
01002	BLI-800	90	1325	116 (27)	Paxil	51
05013	BLI-800	132	211	5064 (44)	Crestor, Zetia	56
09049	BLI-800	447	274	756 (25)	Hyzaar, Toprol XL, ASA	60
17004	BLI-800	692	414	2404 (25)	Simvastatin, fenofibrate	50
18021	BLI-800	665	844	138 (32)	Clonidine, esomeprazole, montelukast, naproxen	61
19021	BLI-800	212	121	684 (33)	Fish oil	44
04009	MoviPrep	953	900	1035 (30)	ASA, terazosin, amlodipine, benzapril	75
05002	MoviPrep	117	109	1682 (21)	none	53
11014	MoviPrep	505	719	8730 (57)	none	45
15024	MoviPrep	53	64	2873 (42)	L-thyroxine	57

ULN = 223 U/L

Data Source: ISS datasets LABS.xpt, CM.xpt, VisDtISS.xpt (VisDtISS.xpt submitted December 23, 2008)



# CK Elevations (2)

Pt	Treatment	Ck, Visit 1	CK, Visit 2	CK, Visit 3	Concomitant Meds	Age	Comments
13039	BLI800	607	107	125 (34)	Dymetadrine	50	Elev. At pre-dose
3063	BLI800	424	618	540 (16)	ASA, fenofibrate,esomeprazole, beconamine,omacor	50	5% elev. In black males
3029	Moviprep	516	659	ND	Insulin, atorvastin	48	
10031	Moviprep	1534	209	101 (32)	Doxazosin,calcium,Vit C &D, saw palmetto,fish oil	65	exercised
13005	Moviprep	104	636	630 (33)	Paracetamol	62	
14007	Moviprep	363	363	630 (33)	Atenolol, olmesartan, medoxomil, amlodipine, dutaseride, HCTZ	64	Uncertain etio.
15025	Moviprep	1437	309	648 (42)	L-thyroxine, ASA, testosterone, quetiapine, somatropin	53	exercised



# Recommendations

## Concerns

- Inadequate quantification of serum sulfates
- Lack of adequate follow-up of electrolytes, CK (fractionated), glucoses, urinalysis, uric acid post-dose
- Lack of follow-up for bradycardia
- Lack of warning labeling for higher risks in subpopulations and populations prone to dehydration, electrolyte changes, renal impairment, tonic-clonic seizures, CHF. Caution with diuretics, ACEI (angiotensin converting enzyme inhibitors), ARB (angiotensin receptor blockers). Restrict use of other laxatives.



# PMR

## Design

- 4 arm AC study of both dose regimens in hundreds of patients
- Sulfate PK pop study with subgroup analysis

## Monitor:

- ECG's, AE's, fractionated CK's, electrolytes (SMA 24), UA, uric acid
- Timepoints: Pre-dose, day of colonoscopy, post-dose (immediately after dose) and past 30 day follow-up



# Exclusion

## Exclusion Criteria

- ileus
- severe UC
- GI obstruction
- gastric retention
- bowel perforation
- toxic colitis
- megacolon
- likely to aspirate
- foreign body removal/decompression
- significant electrolyte abnormalities
- PKU
- h/o renal or hepatic insufficiency
- h/o CHF
- previous GI surgeries
- G-6-PD deficiency

# Definition for elevated TEAE investigations

- “Individual, significant, lab changes defined as greater than 2.5X ULN. Unrelated to study drug-- due to pre-existing conditions or lab errors.
- Pt.4023 Visit 2: LDH=465 (118-273) and AST=51 (13-39). Visit 3 AST=23 and LDH=152 (screen AST=22, LDH=157).
- Pt. 12019 Visit 2: AST=67 (13-39) and ALT=88 (7-52) . Visit 3 AST=22 and Visit 3 ALT= 43 (screen AST=28 and ALT=42).
- Pt. 7021 Visit 2: CK=321 (30-223). Visit 1 and 3 CK=116.



# Bradycardia, potassium changes & concomitant medications (n=3.5-5.1)

Patient ID#	Study	Visit 1 Pulse (bpm)	Visit 2 Pulse (bpm)	Visit 1 K+ (3.5-5.1)	Visit 2 K+	Visit 3 K+	Significant PMH
SuPrep							
2003	S 301	78	53	-----	4.1	3.7	Neurontin, Prozac
3004	S 301	68	54	4.2	4.1	<b>5.6</b>	Dyazide
12023	S 302	72	58	4.5	<b>5.3</b>	4.5	Paxil, Procardia
13032	S 302	73	59	4.9	<b>5.1</b>	4.7	Metformin, Glyburide
15064	S 302	64	56	5.0	4.5	<b>5.2</b>	none
MoviPrep							
8005	M 301	56	47	<b>7.4</b>	4.0		HCTZ
14022	M 302	80	50	4.6	<b>5.1</b>	4.3	none
15015	M 302	60	55	4.9	<b>5.4</b>	4.2	Lisinopril
15040	M 302	55	49	4.9	<b>5.0</b>	4.2	Adalat
18007	M 302	64	53	<b>5.1</b>	4.3	4.5	Altace, Coreg
20017	M 302	76	52	<b>6.5</b>	4.0	4.0	insulin RX
20035	M 302	78	51	4.6	<b>5.2</b>	4.6	none

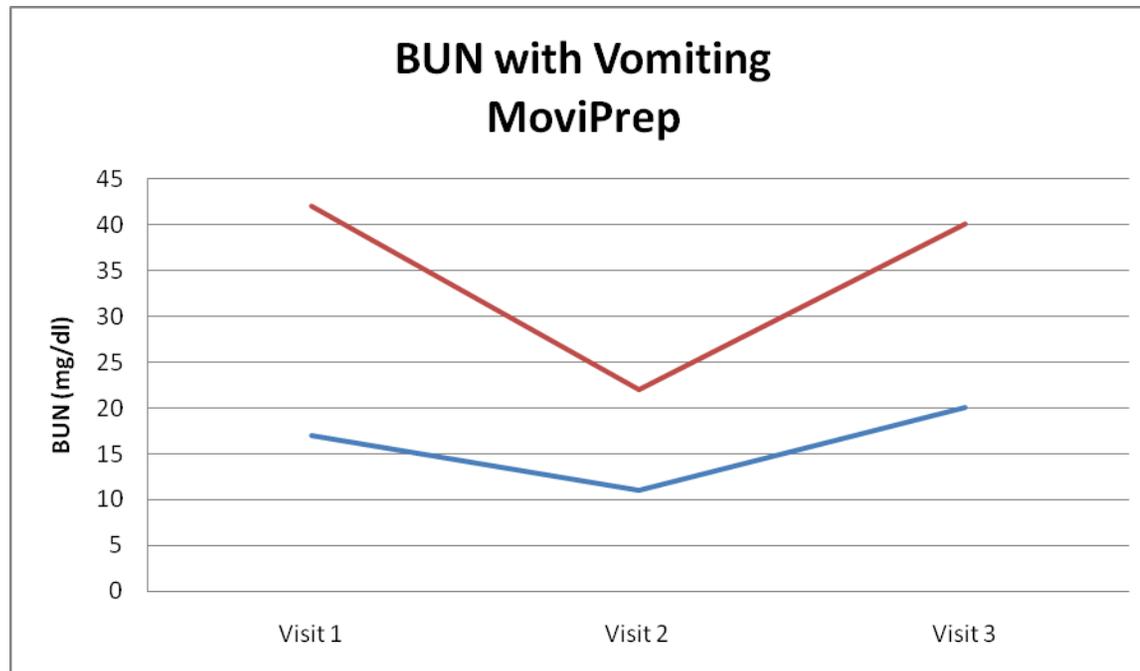


# Uric Acid Changes

	Normal	Drug	Baseline	Visit 2	Visit 3	$\Delta$ to Visit 2	$\Delta$ to Visit 3	P ( $\Delta$ Visit 2)
Uric Acid (mg/dL)	F 2.4-5.7 M 3.4-7.0	Study 301: Suprep	5.67	6.22	5.87	.59	.20	<0.001
		Study 301: Moviprep	5.78	5.78	5.94	-0.01	0.18	
		Study 302: Suprep	5.81	6.27	5.93	0.44	0.14	
		Study 302: Moviprep	5.68	5.70	5.97	-0.02	.28	

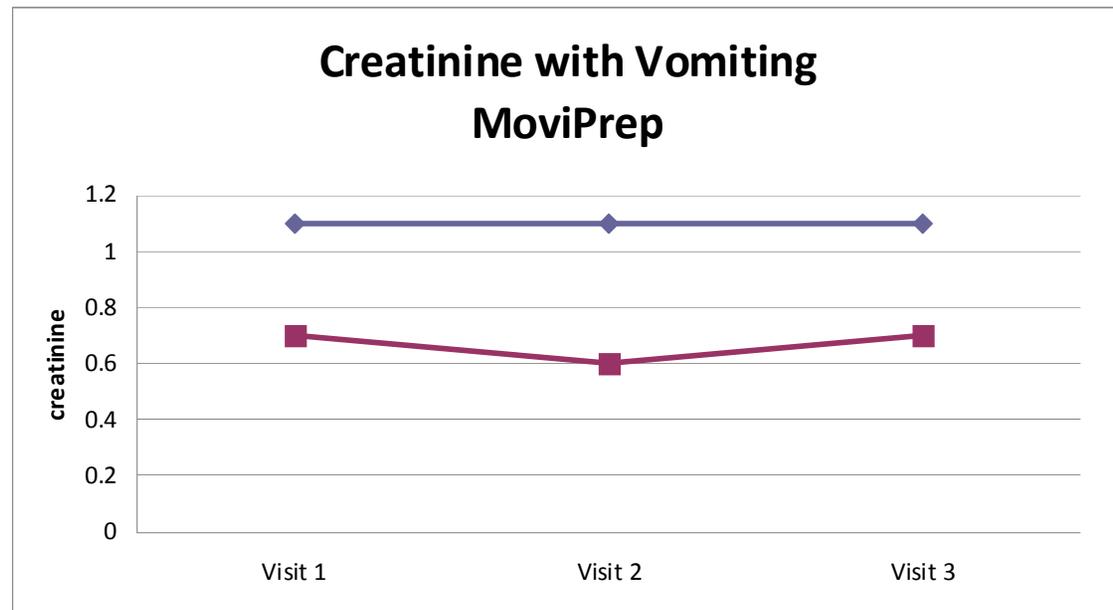
# Moviprep BUN changes with vomiting

- Visit 1=Screening; Visit 2=Day of colonoscopy; Visit 3=Follow-up at 30days





# Creatinine Changes with Vomiting





# Suprep Bowel Prep Kit

## MOTL's Concerns



# Statutory Standard

## FD&C 505(d)(1)

An order refusing to approve the application shall be issued if there is a finding that:

“the investigations ... do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe ....”



# Phase 3 Studies (301 & 302)

## What Tests Were Done?

- About 2 weeks before prep  
VS, serum chemistry, hematology
- After prep, just before colonoscopy  
VS, serum chemistry, hematology, AE
- About 30 days after colonoscopy  
VS, serum chemistry, hematology, AE



# Phase 3 Studies (301 & 302)

## What Tests Were Not Done at All?

- ECG
- U/A with electrolytes
- Orthostatic changes
- Coags



# Phase 3 Studies (301 & 302)

## What Tests Could Have Been Done Better?

- Baseline blood work – closer to time of prep start
  - Increase sensitivity for acute changes
- Systematic assessment of colonoscopic findings
- Follow-up blood work & AEs – additional visit a day or two after colonoscopy
  - Assess extent of acute effects, subclinical renal



# Other Testing in Phase 1 / 2 Program

- Study 202: 6 Normal, 6 Renal, 6 Hepatic
  - Chem, ECG, U/A, PK
  - Only split dose
- Other Early Phase Studies
  - Younger subjects, split dose, not the to-be-marketed product



# Safety Concerns with Osmotic Laxatives

- Risks if used in face of serious GI disease
- Aspiration in those at risk for it
- Fluid and electrolyte abnormalities
- Cardiac arrhythmias, secondarily
- Seizures, secondarily
- Renal injury, secondarily, also nephrocalcinosis with sodium phosphates
- Aphthous ulcers, ischemic colitis

# Nagging Findings with SuPrep

- Renal effects?
  - Nonclinical ? renal tubular effect
  - Patients with mild creatinine increases
  - Increased uric acid
- Bradycardia frequency
  - But not much shift from baseline
- Case of AV block
- Sporadic CK elevations



# Safety Program

## Assessment of Adequacy

- Fluid, electrolyte, renal effects in drug class and suggested in development program
  - U/A with electrolytes, orthostatic VS, F/U for acute creatinine elevation – all are reasonably applicable
- Arrhythmias in drug class
  - ECGs are reasonably applicable
- Aphthous ulcers, ischemic colitis in drug class
  - Systematic colonoscopy assessment is reasonably applicable



# MO TL Tipping Point Deficiencies

- Lack of ECGs
- Lack of U/A with electrolytes
- Lack of acute F/U visit



# MOTL Deficiencies on the Cusp

- No systematic colonoscopic assessment
- No orthostatic VS
- No proximate baseline chemistry testing
- No coagulation tests



## Additional Consideration: Need for Large Safety Database?

- No ICH advice for such one-shot products
- Millions of procedures per year – big public exposure, also lots of patients available
- Most patients are essentially healthy from GI standpoint
- Large number-needed-to-treat begs better determination of uncommon AE rates



# Additional Proposal: Require Large Safety Study

- Minimal entry criteria, testing only per prescriber
- Colonoscopy visit – lab tests, AEs, capture colonoscopy findings, ?ECG
- Follow-up @ 1 month – question of what to include
- If  $\geq 3,000$  patients, could detect 0.1% events

# MOTL's Recommendations for Current Action

- CR citing deficiencies in the safety assessment
- Request studies like the Phase 3 studies, but adding:
  - ECGs
  - Orthostatic VS
  - U/A + electrolytes
  - Coags
  - Systematic colonoscopic assessment
  - Investigation of CK elevations
  - Sulfate levels
  - F/U visit 1-2 days post prep
  - Recommend baseline tests close to prep
  - Require for each regimen proposed for labeling
- Request additional safety study of  $\geq 3,000$  patients.



# Pre- vs. Post-market Requirement?

- Patients are plentiful
- Short participation time
- Deficiencies were several and fundamental



## MOTL's Recommendations if Approved on This Cycle

- Labeling with warnings from any others in drug class, unless evidence otherwise (e.g., no phosphate issue)
- Add language discouraging back-to-back dosing, at least until studied further
- PMR for repeat studies of dosing regimen(s) with added elements as listed on previous slide
- PMR for safety study of  $\geq 3,000$  patients.



# Questions for Discussion



# Question 1

- Should safety investigations be required pre-approval to provide additional safety data for Suprep?

If yes, should these investigations include:

- Repeat of active-controlled Phase 3 trials with additional safety monitoring?
- Large, uncontrolled safety study?



## Question 2

- If no further investigations are required pre-approval, should there be Post-Marketing Requirements (PMRs) for additional safety data?

If yes, should these PMRs include:

- Repeat of active-controlled Phase 3 trials with additional safety monitoring?
- Large, uncontrolled safety study?



## Question 3

- If repeated Phase 3 trials are required (either pre- or post-marketing), what study design elements should be required:
  - ECGs?
  - U/A?
  - Orthostatic vital signs?
  - More intensive safety evaluation between the day of colonoscopy and Day 30? If so, what testing and when?
  - Baseline blood tests closer to the beginning of the prep?
  - Monitoring beyond 30 days?
  - Other?



## Question 4

- If a large safety study is required (either pre- or post-marketing), what should be specified regarding:
  - Size?
  - Duration?
  - Type and intensity of safety monitoring?



## Question 5

- If Suprep is approved without additional pre-market studies, how should this new osmotic laxative be labeled regarding safety?

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22372

-----  
ORIG-1

-----  
BRAINTREE  
LABORATORIES  
INC

-----  
SUPREP BOWEL PREP KIT

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/s/  
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MATTHEW C SCHERER

07/28/2010



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22372	----- ORIG 1	----- BRAINTREE LABORATORIES INC	----- SUPREP BOWEL PREP KIT

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/s/  
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MATTHEW C SCHERER  
08/11/2009

**From:** Simon, Anna Maria  
**Sent:** Thursday, July 30, 2009 11:04 AM  
**To:** 'Caballero, Vivian'  
**Subject:** NDA 22-372 carton and container comments

Dear Vivian,

We have reviewed the revised carton and container labeling you submitted on July 16, 2009, and have the following comment:

Revised labeling of Carton and Bottle [REDACTED] (b) (4)  
[REDACTED] it should be written as "Oral Solution", as stated in your cover letter: "The dosage form has been revised to "Oral Solution".

Please make the above correction and re-submit for final review.

Best regards,  
Anna

Anna M. Simon  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
White Oak BLDG 22, Room 5473

[anna.simon@fda.hhs.gov](mailto:anna.simon@fda.hhs.gov)  
(301) 796-3509 Phone  
(301) 796-9905 Fax

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22372	----- ORIG 1	----- NO FIRM	----- SUPREP BOWEL PREP KIT

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/s/  
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Anna M SIMON  
07/30/2009

**From:** Simon, Anna Maria  
**Sent:** Tuesday, July 21, 2009 12:11 PM  
**To:** 'Caballero, Vivian'  
**Subject:** Regulatory Briefing  
Vivian,

We received a response regarding your request to attend the Regulatory Briefing scheduled for NDA 22-372, Suprep Bowel Prep Kit. Regulatory Briefings are not open to Sponsors; therefore, we need to decline your request.

We will be in contact with you in the upcoming weeks to discuss labeling.

Thank you,  
Anna

Anna M. Simon  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
White Oak BLDG 22, Room 5473

[anna.simon@fda.hhs.gov](mailto:anna.simon@fda.hhs.gov)  
(301) 796-3509 Phone  
(301) 796-9905 Fax

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/s/

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Anna Maria Simon  
7/22/2009 01:54:22 PM  
CSO

Anna Maria Simon  
7/22/2009 01:54:57 PM  
CSO

## MEMORANDUM OF TELECON

DATE: July 20, 2009

APPLICATION NUMBER: NDA 22-372

BETWEEN:

Name: Mark B. Cleveland, Vice President, New Product Development  
Vivian Caballero, Director, Regulatory Affairs  
Claire Walsh, Manager, Regulatory Affairs

Phone: Line provided by sponsor  
Representing: Braintree Laboratories, Inc.

AND

Name:

Donna Griebel, M.D., Division Director  
John Hyde, Ph.D., M.D., Medical Team Leader  
Sushanta Chakder, Ph.D., Supervisory Pharmacologist  
Tamal Chakraborti, Ph.D., Pharmacology Review  
Eric Frimpong, M.A., Ph.D., Mathematical Statistician  
Jane Bai, Ph.D., Pharmacology Reviewer  
Cristi L. Stark, M.S., Acting Chief, Project Management Staff  
Anna Simon, MSN, CPNP, Regulatory Project Manager  
DIVISION of Gastroenterology Products, HFD 180

SUBJECT: Provide notification to the Sponsor that the PDUFA date of August 2, 2009 would be missed, due to the need for a Regulatory Briefing scheduled August 21, 2009.

- The Division informed the Sponsor that the PDUFA date of August 2, 2009 would be missed, due to the need for a Regulatory Briefing scheduled August 21, 2009.
- The purpose for the Regulatory Briefing is for the Division to receive recommendations from Senior Leadership on whether an additional safety study should be conducted pre-approval to provide a more intensive safety evaluation of Suprep in the days before and after the product is administered or if there should be a Post Marketing Requirement safety study if there is an action of Approval.
- The Division informed the Sponsor that in the meantime, work will continue towards an Action to occur soon after the Regulatory Briefing.
- The Sponsor requested to be present at the Regulatory Briefing. The Division responded that this is doubtful due to the confidential discussion that occurs

during a Regulatory Briefing, but that we would consult the Executive Division and notify them of the answer.

- The Division informed the Sponsor that labeling negotiations would continue in the upcoming weeks.
- The Division informed the Sponsor that post marketing required study(s) would be conveyed to them in the upcoming weeks.

---

Anna M. Simon, MSN, CPNP  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22372	----- ORIG 1	----- NO FIRM	----- SUPREP BOWEL PREP KIT

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/s/  
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Anna M SIMON  
07/29/2009



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/s/

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Matthew Scherer  
6/29/2009 11:43:48 AM

**Scherer, Matthew**

---

**From:** Scherer, Matthew  
**Sent:** Tuesday, June 23, 2009 10:22 AM  
**To:** 'Caballero, Vivian'  
**Subject:** NDA 22-372: container/carton comments

Dear Vivian,

We have looked at the revised container and carton labeling you sent via email on 6-12-09 and have the following comments:

- 1) [REDACTED] (b) (4)  
[REDACTED] The entire drug name should be in the same case (i.e., ALL CAPS or All Title Case). This should be revised on the container, carton and booklet.
- 2) The dosage form is "Oral Solution" [REDACTED] (b) (4) This should be revised on the container, carton and booklet.
- 3) Please add parentheses around the list of actives and also around the quantities, i.e., the drug name should be "Suprep Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution (17.5 g/3.13 g/1.6 g) per 6 oz". This should be revised on the container, carton and booklet. Also, this is how the name should be expressed in the Highlights of the Package Insert above the Initial US Approval.

Regards,

**Matthew C. Scherer**  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODEIII  
*Ph: 301-796-2307*  
*Fax: 301-796-9905*

10903 New Hampshire Avenue  
Building 22, Room 5137  
Silver Spring, MD 20993

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/s/

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Matthew Scherer  
6/23/2009 10:26:27 AM  
CSO



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) Oral solution.

We are reviewing the immediate container and carton labeling submitted with your NDA and has the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

Container Label

1. The proprietary name submitted contains a capitalized ‘P’ in the middle of the name. We believe that the capitalization of the letter ‘P’ in the proposed name, SuPrep Bowel Prep Kit, will vary in practice. Thus, we request the name be revised so that the ‘p’ is in lower case.
2. Each bottle should emphasize that two separate doses are necessary for treatment. (b) (4)
3. The label should indicate that further dilution is required prior to ingesting the liquid.
4. The container label should indicate the corresponding strengths of each ingredient (i.e., Suprep Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution (17.5 g/3.13 g/1.6 g) per 6 oz) in accordance with CFR 21 201.57 (c) (4).
5. Remove the statement, ‘Prescription Bowel Prep’ from the primary display panel as it is duplicative and crowds label.
6. “Suprep Bowel Prep Kit” should appear in the same font and color.

Carton Labeling

7. (b) (4)

8. [REDACTED] (b) (4)
9. The carton label should indicate that further dilution is required prior to ingesting the liquid. We recommend this information be included on panels 1 and 4.
10. The carton labeling should indicate the corresponding strengths of each ingredient (i.e., Suprep Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution (17.5 g/3.13 g/1.6 g) per 6 oz) in accordance with CFR 21 201.57 (c) (4).
11. The product name, "Suprep Bowel Prep Kit" should appear in the same font size, style and color.
12. [REDACTED] (b) (4)
13. On Panel 1, patients should be advised to read the [REDACTED] (b) (4) at least 2 days before the scheduled procedure.
14. On Panels 1 and 4, the [REDACTED] (b) (4) should be removed.
15. [REDACTED] (b) (4)
16. On Panel 2, add a statement informing patients what they can eat and drink on day of procedure.
17. On Panels 2 and 4, [REDACTED] (b) (4) should be changed to 'mixing container'.
18. On Panel 2, [REDACTED] (b) (4) change [REDACTED] (b) (4) to "over the next hour".
19. Please clarify the contents and structure of the enclosed booklet referenced on Panel 4.
20. Ensure that the instructions for use on Panel 5 are consistent with those on the package insert.
21. [REDACTED] (b) (4)

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

-----  
Cristi Stark  
5/27/2009 10:23:41 AM



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) oral solution.

We also refer you to your submissions dated August 22, 2008, August 28, 2008, September 11, 2008, October 27, 2008, November 20, 2008, December 11, 2008, December 23, 2008, January 22, 2009, February 9, 2009, February 20, 2009, March 6, 2009, April 2, 2009, April 20, 2009, April 29, 2009, May 5, 2009 and May 13, 2009.

We have the following comments and requests for information. We request a prompt written response in order to continue our evaluation of your NDA.

1. In reference to your April 20, 2009 submission, re-submit, as xpt files, the safety data for Tables in 14.3.1A-14.3.5A for individual studies 301 and 302 and combined studies 301 and 302 so they include non-ITT patients in addition to ITT patients (i.e., all of the randomized patients in the study arm). For example, the sample size (N) for Study 301 for BLI800 should be 204 rather than 194 and for the MoviPrep arm 204 rather than 193. Re-submit the subgroup analyses requested by the FDA on April 14, 2009 (item #4) in a similar manner.
2. Also, note that your response to item #1 of the April 29, 2009 information request dated should also include both ITT patients and non-ITT patients as your N for Study 301 and 302 and combined datasets. Please resubmit.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, RPh, MBA  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Brian Strongin  
5/22/2009 11:47:27 AM



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) oral solution.

We also refer you to your submissions dated August 22, 2008, August 28, 2008, September 11, 2008, October 27, 2008, November 20, 2008, December 11, 2008, December 23, 2008, January 22, 2009, February 9, 2009, February 20, 2009, March 6, 2009, April 2, 2009, and April 20, 2009.

We have the following comments and requests for information. We request a prompt written response in order to continue our evaluation of your NDA.

1. Datasets AE.xpt and SY.xpt for adverse events such as vomiting, submitted January 22, 2009, are not compiled in a total adverse events table. For instance, Table 302-10 (BLI800 group) lists 15 patients with vomiting among all mild, bothersome, distressing or severely distressing ratings, yet, in Table 302-8 TEAE (BLI800 group), only 1 patient was listed -- far less reports of vomiting.

Provide a dataset that augments the AE.xpt dataset with adverse events from the SY.xpt file so that the new dataset also includes all the cases of cramping, stomach bloating, nausea, vomiting and overall discomfort coded in MEDRA terminology and so that ALL adverse events are accounted for, regardless of severity. Include all mild, bothersome, distressing, or severely distressing ratings for all gastrointestinal symptoms from both the symptom questionnaires and your TEAE events.

2. Table 14.3.1A on page 68 of your April 20, 2009 submission, lists 274 and 277 treatment emergent adverse events (TEAEs) for BLI800 and MoviPrep, respectively under the "gastrointestinal disorders" Body System. The individuals sums of just two of the symptoms - the abdominal distension and abdominal pain categories - exceed this sum. Clarify if the SY.xpt (Symptom questionnaire) descriptions of Abdominal cramping and Abdominal bloating were included under one of these terms and then re-tabulate and re-submit this table. Are there any additional adverse events that are to be submitted to this NDA that have yet to be included?
3. Study 301 and 302 had serum samples collected from patients. You state that serum sulfate tests were not performed on these samples. Clarify whether these samples have been preserved and, if so, if they can be analyzed for serum sulfate.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Cristi Stark  
4/29/2009 08:30:59 AM



NDA 22-372

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SuPrep (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) oral solution.

On April 21, 2009, we received your April 20, 2009 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 2, 2009.

If you have any questions, call me at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Matthew Scherer, MBA  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Matthew Scherer  
4/28/2009 09:11:34 AM



NDA 22-372

INFORMATION REQUEST LETTER

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We also refer you to your submissions dated August 22, 2008, August 28, 2008, September 11, 2008, October 27, 2008, November 20, 2008, December 23, 2008, January 22, 2009, February 9, 2009, February 20, 2009, March 6, 2009 and April 2, 2009.

We have the following requests for information. We request a prompt written response in order to continue our evaluation of your NDA.

- 1. Provide clarification similar to your recent Summary of Screen Failures, submitted April 2, 2009, on your other drop-out patients. The datasets, submitted January 22, 2009, have been carefully reviewed and the two sections in Module 5 Volume 9.3 and 10.3 have been reviewed for protocol violations. Detailed descriptions of the reasons for discontinuation of the Non-ITT and the ITT Non-completers (approximately 42 patients) categorized as "did not meet criteria" "withdrew consent" "non-compliance" and "adverse events" should be correlated with 1) whether they received any of their medication (and whether they completed the prep), 2) whether they received the colonoscopy (if applicable), and 3) whether they had Visit 3. If they did not continue in the study, please indicate when they were discontinued. Present this information in a table that includes columns such as patient identifier, age, gender, ITT status, when medication dispensed, when scope completed, reason for discontinuation -- description, during which visit the patient dropped out.

For example, use the following column headings:

Patient ID	age	sex	Study	Treatment group	ITT completer	ITT non-completer	Non-ITT	Full/partial drug treatment (F or P)	Visit 2 labs done
Colonoscopy done	Visit 3 done	Detailed reason for discontinuation (did not meet criteria, withdrew consent, non-compliance, AE, lost to F/U)				When drop-out occurred (before or After Visit 2 or Visit 3)			

2. Generate a dataset for patients in Study 301 and Study 302, in a combined dataset but identifying individual studies, of patients who had pulses less than 60 beats per minute on Visit 1 and subgrouped to those with pulses less than 50 bpm (place in rows). The patient identifier numbers, ages, and treatment group, study group, concomitant medications, and adverse events should be in columns. Prepare 3x3 transition contingency tables showing the percentages of changes from non-bradycardic to bradycardic patients, and vice versa, in each treatment group during Visit 1 vs. Visit 2, using the categories of normal, <60 and <50. Present the tables for each treatment group for each study and for the treatment groups for the studies combined. Make sure the denominators (n= number of randomized patients that includes all patients who were given drug except the screen failures who were not given study drug) accounts for all randomized patients are used.
3. We received your April 2, 2009 response to our question about the serum sulfates for Study 301 and Study 302 that were included in your protocol. These serum samples were apparently drawn as part of the protocol, but, not analyzed. You state that results for BLI800-202 study confirmed that additional sulfate testing was not required. In addition, you did not file a formal amendment to the IND. Explain on what basis, where, and by whom this agreement to not have the Phase 3 serum sulfates analyzed is documented. Please direct us to or enclose the minutes or other correspondence that verify FDA concurrence with this decision.
4. Provide tables of all your adverse events in your treatment group and non-treatment group including all those rated as "mild", "moderate", "severe" or "fatal". You state that you excluded the gastrointestinal symptoms that were not rated as "severe" in Table 301-8 and other tables. Therefore, in a separate table, list the included patients by identifier number who had the mild, moderate, etc., categories that you added to the gastrointestinal category that you did not list in your original submission under TEAE.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Cristi Stark  
4/14/2009 01:56:10 PM

## Scherer, Matthew

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**From:** Scherer, Matthew  
**Sent:** Wednesday, April 01, 2009 3:56 PM  
**To:** 'Caballero, Vivian'  
**Subject:** Suprep (NDA 22-372) Clarifications

Vivian,

As discussed during a phone call this afternoon, a couple of questions have recently come up during the review of the SuPrep NDA:

- It is unclear if the serum sulfates you had planned to analyze in patients were ever done. If they were done, please supply the data. If they were not done, please provide explanation of why this was not performed as listed in the protocol.
- Please clarify what patient self-administration instructions for the same day and split-dose regimens and dietary requirements were used during the study (i.e., the actual sheets the patients would have received at the study sites upon inclusion in the study). Were these included in the submitted materials? If so, please indicate where they can be found.
- Please clarify your intentions regarding [REDACTED] (b) (4) Will there be a [REDACTED] (b) (4) [REDACTED] ?
- In the BLI800-301 study, please identify which of the patients you call "Screen Failures" actually were dispensed medication and when they received the medication. Of the 5 patients included in the "did not meet criteria" category and of the 3 patients that were included in the "withdrew consent category", please list the patient by identifier and the reasons for each patient's screen failure (we have reviewed the dataset and request your descriptions to be more detailed).

Please respond to the above items as soon as possible. I would appreciate any feedback on the labeling questions by 12:00 tomorrow (Thursday) so we can discuss at an afternoon meeting.

Best regards,

Matt

-

**Matthew C. Scherer**  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODEIII  
*Ph: 301-796-2307*  
*Fax: 301-796-9905*

10903 New Hampshire Avenue  
Building 22, Room 5137  
Silver Spring, MD 20993

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/s/

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Matthew Scherer  
4/13/2009 12:39:25 PM  
CSO



NDA 22-372

**ADVICE LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) (b) (4) Oral Solution.

The following issues/deficiencies have been identified in your proposed labeling. Please address these issues as soon as possible.

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 (b) (4)
- 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 package insert emailed to Matthew Scherer on March 18, 2009, but not in the submitted SPL. You must include this statement in the SPL label. [See 21 CFR 201.57(a)(3)]
- Remove the (b) (4) subsection.
- Use command language whenever possible (e.g., “...perform appropriate studies to rule out...” rather than (b) (4)) throughout the label. 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; revise to make it more concise.
- The presentation of adverse event criteria in the ADVERSE EVENTS subsection must be expressed as an incidence rate greater than X%. In the statement “Most common adverse event reactions ( (b) (4) are abdominal distension...”, change (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 Section

- Add a period (“.”) to the statement: “Sections or subsections omitted from the full prescribing information are not listed”.

#### Full Prescribing Information Section

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

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Cristi Stark  
3/27/2009 03:19:26 PM



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please submit the following information:

1. Revised drug product specification to (1) Include the Identification tests for Sulfate, Sodium, Potassium and Magnesium and (2) (b) (4) the assay limit for Benzoate (b) (4) .
2. Certificates of analysis for Sodium (b) (4) and Potassium (b) (4) reference standards. Provide the re-test (expiration) period information of these reference standard solutions.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Moo-Jhong Rhee  
3/3/2009 05:49:09 PM  
Chief, Branch III



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We also refer you to your submissions dated August 22, 2008, August 28, 2008, September 11, 2008, October 27, 2008, November 20, 2008, December 23, 2008, and January 22, 2009.

We have the following requests for information. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the patients who experienced Serious Adverse Events (SAEs) during the Phase 3 clinical trials, we acknowledge receipt of the case report forms (CRFs) for these events in your November 20, 2008 submission; however, we are unable to locate the narratives for two of the three patients who experienced these SAEs, including:
  - a. Patient 20013, who experienced respiratory distress
  - b. Patient 12002, who experienced non-cardiac chest pain

Direct us to the location of these narratives in the NDA submission. If no narratives were submitted for these SAEs, then submit narratives or MedWatch report forms to the NDA for each of these patients, which describe these events in detail.

2. Clarify the patient identifier number for one patient for whom there appears to be a discrepancy. In the CRFs submitted November 20, 2008, the patient is listed as patient 5013; however, in the (b) (4) laboratory sheets with the CRFs, the patient is listed as patient 5113. Please clarify whether this is the same patient, and, if so, which number is the correct patient identifier.
3. For the ISS Adverse Event (AE) dataset (AE.xpt), submitted January 22, 2009, in which the AEs from the two Phase 3 clinical studies were pooled, we have generated an AE incidence table from the data provided in the dataset, as follows (see Table 1):

**Table 1: AE incidence table derived from ISS AE.xpt dataset**

<b>Treatment Group</b>	<b>Total</b>	<b>BLI-800</b>	<b>Moviprep</b>
<b>N =</b>	<b>770</b>	<b>388</b>	<b>382</b>
<b>AEDECOD</b>	<b>n(%)</b>	<b>n(%)</b>	<b>n(%)</b>
NAUSEA	14 (2)	6 (2)	8 (2)
HEADACHE	10 (1)	6 (2)	4 (1)
VOMITING	9 (1)	6 (2)	3 (1)
ABDOMINAL DISTENSION	8 (1)	5 (1)	3 (1)
ABDOMINAL PAIN	8 (1)	5 (1)	3 (1)
CHILLS	4 (1)	2 (1)	2 (1)
ANAL DISCOMFORT	3 (<1)	1 (<1)	2 (1)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (<1)	2 (1)	0
NASOPHARYNGITIS	2 (<1)	2 (1)	0
ABDOMINAL PAIN UPPER	1 (<1)	0	1 (<1)
ALANINE AMINOTRANSFERASE INCREASED	1 (<1)	1 (<1)	0
ANXIETY	1 (<1)	0	1 (<1)
ATRIOVENTRICULAR BLOCK COMPLETE	1 (<1)	1 (<1)	0
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (<1)	1 (<1)	0
BLOOD LACTATE DEHYDROGENASE INCREASED	1 (<1)	1 (<1)	0
BLOOD URINE PRESENT	1 (<1)	1 (<1)	0
BRADYCARDIA	1 (<1)	0	1 (<1)
COLITIS ISCHAEMIC	1 (<1)	0	1 (<1)
DIARRHOEA	1 (<1)	1 (<1)	0
DISCOMFORT	1 (<1)	0	1 (<1)
DIZZINESS	1 (<1)	0	1 (<1)
DRY MOUTH	1 (<1)	1 (<1)	0
DYSURIA	1 (<1)	1 (<1)	0
FEELING HOT	1 (<1)	0	1 (<1)
INFLUENZA	1 (<1)	0	1 (<1)
KIDNEY ENLARGEMENT	1 (<1)	1 (<1)	0
LARGE INTESTINE PERFORATION	1 (<1)	0 (0)	1 (<1)
MOUTH ULCERATION	1 (<1)	1 (<1)	0
NON-CARDIAC CHEST PAIN	1 (<1)	0	1 (<1)
PRURITUS	1 (<1)	1 (<1)	0
RESPIRATORY DISTRESS	1 (<1)	0	1 (<1)
SINUS TACHYCARDIA	1 (<1)	0	1 (<1)
URINARY TRACT INFECTION	1 (<1)	1 (<1)	0

We note, however, that the incidence rates in this table do not agree with the rates in your AE incidence table in the NDA submission (located in Module 2, Volume 1.1 under tab 2.7 in the original submission). Clarify the discrepancies noted for some of the AE preferred terms between the two tables.

4. Upon review of the ISS laboratory values dataset (LABS.xpt), submitted January 22, 2009, in which the safety laboratory results from the two Phase 3 clinical studies were pooled, we note several instances in which patients experiences creatine kinase (CK) elevations (elevation defined as >3 X ULN), as follows (see Table 2):

**Table 2: Patients in Phase 3 studies with post-treatment CK elevations >3 X ULN**

PT	TREATC	Screening visit CK, U/L	Visit 2 (colonoscopy) CK, U/L	Follow-up visit CK, U/L (post- treatment day)	Concomitant medications	Age (yrs)
01002	BLI-800	90	1325	116 (27)	Paxil	51
05013	BLI-800	132	211	5064 (44)	Crestor, Zetia	56
09049	BLI-800	447	274	756 (25)	Hyzaar, Toprol XL, ASA	60
17004	BLI-800	692	414	2404 (25)	Simvastatin, fenofibrate	50
18021	BLI-800	665	844	138 (32)	Clonidine, esomeprazole, montelukast, naproxen	61
19021	BLI-800	212	121	684 (33)	Fish oil	44
04009	MoviPrep	953	900	1035 (30)	ASA, terazosin, amlodipine, benzapril	75
05002	MoviPrep	117	109	1682 (21)	none	53
11014	MoviPrep	505	719	8730 (57)	none	45
15024	MoviPrep	53	64	2873 (42)	L-thyroxine	57

ULN = 223 U/L

Data Source: ISS datasets LABS.xpt, CM.xpt, VisDtISS.xpt (VisDtISS.xpt submitted December 23, 2008)

We additionally note that in "Laboratory Abnormalities" in Module 5, Volume 9.3, tabs 16.2.20.1 and 16.2.20.2 and Module 5, Volume 10.3 tabs 16.2.20.1 and 16.2.20.2 of your NDA submission, you note a number of elevated CKs; however, no discussion of the etiology of these elevations is provided. Provide justification as to why these values may have been elevated, such as concomitant medications (e.g., statins), patient activity or other causes that may have contributed to these elevations, or other relevant patient information that may explain these results.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Cristi Stark  
2/18/2009 06:54:39 AM



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following information on the Drug Substances:

1. Storage conditions and container/closure description used for the stability study of the following lots:
  - Potassium Sulfate: (b) (4), Lot # 9144, 9145 and 9146 (3.2.S.7.3)
  - Magnesium Sulfate: (b) (4) Lot # E34174, C29144 and B24155 (3.2.S.7.3)
2. Updated stability tables (2008 stability results) for the above listed Magnesium Sulfate batches

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Moo-Jhong Rhee  
2/6/2009 10:11:52 AM  
Chief, Branch III



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We also refer you to your submissions dated August 22, 2008 and August 28, 2008, September 11, 2008, October 27, 2008, November 20, 2008 and December 23, 2008. We additionally refer to the teleconference held between representatives of the Division of Gastroenterology Products and Braintree Laboratories, Inc. on January 15, 2009. As discussed during the teleconference, you agreed to provide the following:

1. For the ISS-ISE datasets folder where the datasets for Studies BLI800 301 and 302 have been pooled, the datasets lack columns that would allow for the calculation of dates of interest for the review. For example, in the AE.xpt dataset, the event occurrence date ("DCMDATE") and AE start date ("AESTDTC") columns are in character format, and there is no column for date of administration of study medication. Thus, we are unable to calculate the date of occurrence of the AE from the time of study medication administration. Similar problems are noted in all of the datasets (e.g., labs.xpt, treat.xpt, sy.xpt). Submit revised datasets (as xpt files) for the ISS-ISE folder with the date information columns in numeric date format, where applicable, and a column for the date of administration of study medication. Also add a column in the AE.xpt file that calculates the number of days between the day of administration of study medication and the adverse event start day.
2. In the AE.xpt dataset definitions file, in the SAE occurrence column ("SAEOCCUR"), you have designated the occurrence of an SAE as 1=yes and 2=no. However, analysis of the number of SAEs in this column does not appear to be accurate. That is, only one SAE appears as a "yes" (patient 12002, atypical chest pain), and 68 rows have no designation, including at least two additional rows that may be SAEs (patient 02032, nausea, and patient 20013, death). You should clarify how many SAEs occurred during Studies BLI800 301 and 302, which should include the recently reported patient with the colonic perforation, and clarify how this information can be accurately extracted from the dataset.

Upon further review of the clinical section of your NDA, we have the following additional information request. We request a prompt written response in order to continue our evaluation of your NDA.

3. Under clinical item #4 of submission dated November 20, 2008, you state, "During a routine review of the statistical programming used to generate analyses for the Phase III studies supporting NDA 22372, a minor programming error was detected which affects some of the adverse event tables for study BLI800-302 and the Integrated Summary of Safety." You should re-submit these changes as new xpt/SAS files and hard copies, not simply as revisions in an addendum.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Cristi Stark  
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/s/

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Matthew Scherer  
12/23/2008 10:51:39 AM



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution. We also refer you to your submissions dated August 22, 28, September 11, October 27, and November 20, 2008.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

SOLUTION 4

We have received your explanation of the Solution 4 study. We understand that you did not conduct these studies, the results from the Solution 4 studies were "not pursued further", and there was only one patient studied. However, we ask that you include electronic and paper Solution 4 laboratory datasets (including the demographics, serum electrolyte results for sulfate solutions, symptoms, urine electrolyte results for sulfate solutions and stool scatocrit, stool electrolyte results for laxatives & sulfate solutions) from each time point drawn and any symptoms, even mild, that were associated with Solution 4. In particular, please describe which adverse events were seen, since data appear for Solution 4 in Table 4: Mean Stool Volume Output (mL) Single- Dose Sulfate formulations on p. 012 and Figure 1: % Stool Solids on p. 013. The same datasets that you enclosed for the other Solutions will be reviewed for safety parameters.

DRUG ADMINISTRATION and FOLLOW-UP VISIT DATES

Your data tabulations provide the date the drug was dispensed, but do not identify the actual day the patient took the treatment. Some subjects were given the study drug on the "date administered" but did not have a colonoscopy and therefore did not ingest the drug until weeks later. We require information about the date that the treatment was ingested by each subject in studies BLI-301 and BLI-302. Please provide a table displaying date drug dispensed, date

ingested, date of colonoscopy, date of Visit 2, and date of Visit 3 for each subject in each of those two studies. Please provide the data as a paper tabulation as well as in electronic datasets that can be merged into the previously submitted datasets. Please also include variables providing the number of days between the date dispensed to date of ingestion, date of colonoscopy to Visit 2, and date of colonoscopy to Visit 3.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey  
12/5/2008 11:12:03 AM



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following information on the Drug Substances:

Potassium Sulfate (Ph.Eur; FCC):

- As mentioned in Section 3.2.S.2.4 “The manufacturer, (b) (4), has reportedly performed a Hazard Analysis and Critical Control Points of the entire process, (b) (4)”. Please provide the details of the critical control points.
- Please add an FT-IR identification test to the specification of the drug substance.
- Please submit a certificate of analysis issued by the drug substance manufacturer (b) (4)
- Please provide detailed information on the primary storage container system with relevant citations of the 21 CFR requirements.

Magnesium Sulfate (USP):

- Please identify the supplier(s) of the starting materials for the synthesis of  $MgSO_4$  (anhydrous) and provide all certificates of analysis for these starting materials.

- Please add an FT-IR identification test to the specification of the drug substance.
- Please provide detailed information on the primary storage container system, with relevant citations of the 21 CFR requirements.
- Please define the retest period for unopened drug substance.
- Please verify that the Product Code 5053 represents the grade of this drug substance as “Intended for use in preparing non-parenteral dosage forms”.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee  
Branch Chief  
Division of Pre-Marketing Assessment II (DPA II)  
Center for Drug Evaluation and Research

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/s/

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Moo-Jhong Rhee  
11/17/2008 11:29:17 AM  
Chief, Branch III



NDA 22-372

**INFORMATION REQUEST LETTER**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director, Regulatory Affairs  
60 Columbian Street West  
P.O. Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your July 1, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution. We also refer you to your submissions dated August 22, 28, and September 11, 2008.

We are reviewing the Statistical and Clinical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Statistics

- 1) You have proposed a 15% non-inferiority margin without sufficient justification. Provide a more detailed justification on the selection of a non-inferiority margin of 15%.
- 2) Please resubmit the SAS datasets and include study number, treatment group, age, and gender.
- 3) Please submit the following new efficacy datasets:
  1. Primary efficacy dataset
  2. Secondary efficacy dataset

These datasets should contain the following variables:

1. unique patient ID
2. center number
3. race
4. age
5. gender
6. treatment group

7. day (i.e., visit decoded) where zero denotes the time of randomization  
Note: this variable is present when the data were collected at several visits; it will be missing when there is only one record per patient
8. other important demographic/prognostic variables
9. last day completed for the patient
10. randomized (1= patient randomized, 0= patient not randomized)
11. completer? (1=yes patient completed whole study, 0=patient discontinued early)
12. reason (reason for patient discontinued)
13. ITT (1=patient in ITT analysis, 0=patient not in ITT analysis)
14. Per protocol? (1=patient in per protocol analysis, 0=patient not in per protocol analysis)
15. LOCF indicator variable (1=record contains the last efficacy value on study; 0=not the last value)
16. raw and derived data for the efficacy variables:
  - derived data (e.g., change from baseline)
  - baseline should be included with each record as well as for the time 0 record
  - the value at that visit

Please follow the guidance for the submission of electronic data. This guidance may be found at: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm> (see Study Data Specifications).

### Clinical

4) Please submit the following case report forms (CRFs):

Death (Moviprep): 20013

Serious AEs (Moviprep): 12002, 11007, 20013

Markedly abnormal creatine kinase (CK) in BLI-800-301 and BLI-800-302:

Treatment group: 1002, 5013, 13039, 12002, 3063, 9049, 17004, 18021, 19021  
Moviprep group: 3029, 4009, 5002, 9035, 10031, 15024

Abnormal glucoses in BLI-800-301 and BLI-800-302:

Treatment group: 2001, 3032, 5004  
Moviprep group: 2008, 3042, 10054

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, MPH  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maureen Dewey

11/12/2008 12:34:27 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): **Sylvia Gantt, OPS, Microbiology Review**

FROM (Name, Office/Division, and Phone Number of Requestor): **Matthew Scherer, RPM, Div of Gastroenterology Products, 301-796-2307**

DATE  
9/19/08

IND NO.  
NA

NDA NO.  
22-372

TYPE OF DOCUMENT  
New NDA

DATE OF DOCUMENT  
July 1, 2008

NAME OF DRUG  
SUPREP

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
cathartic/laxative

DESIRED COMPLETION DATE  
January 31, 2009

NAME OF FIRM: **Braintree Laboratories, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW                  |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY                      |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS                  |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |  |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** The Division of Gastroenterology and ONDQA would like to consult OPS for assistance reviewing a Microbiological attributes and Preservative Effectiveness (PE) study for NDA 22-372 (SUPREP). This is a paper NDA received July 2, 2008 with a PDUFA date of May 2, 2009. The Micro and PE study is located in Section 3.2.P.2.5, which will be delivered to your office by the end of this week. If you have any questions, please call Matt Scherer, RPM at 6-2307 or Tarun Mehta, CMC Reviewer at 6-1712.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Matthew Scherer  
9/23/2008 04:43:20 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-372

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director of Regulatory Affairs  
60 Columbian Street West  
PO Box 850929  
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your new drug application (NDA) dated July 1, 2008, received July 2, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for SUPREP (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We also refer to your submissions dated August 22, 2008, and August 28, 2008, providing more detailed indexing, a revised table of contents and electronic datasets for your Phase 3 trials.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 2, 2009.

We request that you address the following issues:

- 1) Submit electronic datasets for studies: Baylor 001-022, Baylor 006-181, Baylor 005-082, BLI-201, BLI-101, and any other sets not completed for BLI-202, 301, 302.
- 2) Under volume 8.1, tab 5.3.5.3, there is a list of data tabulations and there is no ISE and ISS as described in *eCTD Guidance for Industry: Integrated Summary of Effectiveness* (August 2008) and *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (June 2007). Submit an ISE and ISS as described in those guidance documents.
- 3) Clarify if the date the test drug given is the date the pharmacy filled the drug, the date introduced into study, or the date the drug was prepared. Example: Module 5, volume 10.4, July 25, 2007, is provided on page 1518 and July 24, 2007, is provided on page 1699. It is unclear what these dates (and other similar dates) refer to.

- 4) Clarify the purpose and use of the audit history reports:
  - Module 5, volume 10.4., pages 1520 to 1674 and pages 1701 to 1728.
  - Module 5, volume 9.4., pages 1597 to 1633, pages 1665 to 1719, pages 1758 to 1859, and pages 1898 to 1985.
- 5) Potassium sulfate is not included in the USAN (U.S. Adopted Names) dictionary. You will need to file an application with the USAN Council for the established name of this drug substance.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients aged birth to 16 years.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Richard W Ishihara  
9/12/2008 12:21:25 PM

# REQUEST FOR CONSULTATION

TO (Division/Office):

**CDER OSE CONSULTS**

FROM: Matthew C Scherer, RPM, Division of  
Gastroenterology Products, 6-2307

DATE 9-5-08	IND NO.	NDA NO. 22-372	TYPE OF DOCUMENT New NDA submission	DATE OF DOCUMENT 7-1-08
NAME OF DRUG SUPREP		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG cathartic/laxative	DESIRED COMPLETION DATE 2-2-09

NAME OF FIRM: Braintree Laboratories, Inc.

## REASON FOR REQUEST

### I. GENERAL

<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE--NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END OF PHASE II MEETING	<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> SAFETY/EFFICACY	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION	<input type="checkbox"/> CONTROL SUPPLEMENT	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b>
<input type="checkbox"/> MEETING PLANNED BY		

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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### IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS: DGP has received an NDA for the bowel cleansing preparation SUPREP to be sold as SUPREP® BOWEL PREP KIT. This consult is a request for a tradename and container/carton review. The proposed PI and container and carton labels are attached. Please contact Matt Scherer (301-796-2307) with any questions.

**PDUFA DATE: 5-2-09**

**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA IND 74,808

HFD-180/Division File

HFD-180/RPM

HFD-180/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER Matthew Scherer, 6-2307	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

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/s/

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Matthew Scherer  
9/8/2008 12:01:34 PM



NDA 22-372

**NDA ACKNOWLEDGMENT**

Braintree Laboratories, Inc.  
Attention: Vivian Caballero  
Director of Regulatory Affairs  
60 Columbian Street West  
PO Box 850929  
Braintree, MA 02185

Dear Ms. Cabellero:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Suprep (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution

Date of Application: July 1, 2008

Date of Receipt: July 2, 2008

Our Reference Number: NDA 22-372

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 31, 2008 in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the

certification requirement. The form may be found at:  
<http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at:  
[http://internet-dev.fda.gov/cder/regulatory/FDAAA\\_certification.htm](http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm). Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastroenterology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-2307.

Sincerely,

*{See appended electronic signature page}*

Matthew Scherer  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Matthew Scherer

7/16/2008 04:40:45 PM

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** March 26, 2007  
**TIME:** 3:00PM  
**LOCATION:** White Oak Building #22, Conference Room 1415  
**APPLICATION:** IND 74,808  
**DRUG NAME:** Oral Sulfate (magnesium, sodium, potassium) Solution  
**TYPE OF MEETING:** Type B

**MEETING CHAIR:** Ruyi He, M.D.

**MEETING RECORDER:** Brian Strongin, R.Ph., M.B.A.

**FDA ATTENDEES:** (Title and Office/Division)

<b>FDA Attendee</b>	<b>Title</b>	<b>Office/Division</b>
Ruyi He, M.D.	Medical Team Leader	Division of Gastroenterology Products
Keith St. Amand, M.D.	Medical Officer	Division of Gastroenterology Products
Mike Welch, Ph.D.	Team Leader, Biometrics	Division of Biometrics 3
Sushanta Chakder, Ph.D.	Pharmacology/Toxicology Reviewer	Division of Gastroenterology Products
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff	Division of Gastroenterology Products

**Braintree Laboratories ATTENDEES:**

<b>ATTENDEE</b>	<b>TITLE</b>
Mark vB. Cleveland, Ph.D.	Vice President, New Product Development
Vivian A. Caballero	Director, Regulatory Affairs
John McGowan	Clinical Operation Manager
Claire Polleys	Manager, Regulatory Affairs

**BACKGROUND:**

IND 74,808 for Oral Sulfate (magnesium, sodium, potassium) Solution was submitted April 10, 2006 to provide gastrointestinal lavage prior to colonoscopy. On January 11, 2007 Braintree submitted a request for an end-of-phase 2 meeting to discuss the recently completed phase 1 and phase 2 studies, to reach agreement on the design of the phase 3 clinical protocols to support the planned NDA submission, and to discuss pharmacology/toxicology and chemistry, manufacturing, and controls aspects of the drug development program.

**MEETING OBJECTIVES:**

1. Determine if the agency will require additional pharmacology/toxicology studies in support of an NDA for Oral Sulfate Solution.
2. Obtain agreement from the agency on the number of studies and study design of the proposed phase 3 studies that will be conducted in support of an NDA for Oral Sulfate Solution.
3. Identify any additional deficiencies in the proposed development plan.

**DISCUSSION POINTS:****CMC Section**

The product will be supplied as a liquid formulation in two plastic bottles (about 4 ounces each) along with a plastic 16 oz measuring cup and administration instructions. The patient will be instructed to add one bottle of flavored Oral Sulfate Solution to the cup and then fill to a 16 oz line with water. After drinking the Oral Sulfate Solution, the patient will be instructed to drink an additional two 16 oz cups of water. After waiting (b) (4) overnight) the patient will repeat the above procedure using the second bottle of Oral Sulfate Solution.

- 1) What microbiological testing should be performed?
- 2) Are there any other CMC issues that we should pay special attention to?

**Response to 1 and 2:** Prior to initiating Phase 3 trials you need to define your full formulation. This should be the same formulation you intend to market. The flavoring agents and (b) (4) the sodium sulfate, magnesium sulfate, and potassium sulfate will need to be identified. You will likely need to include (b) (4) in the formulation. Please refer to ICH Guidance Q6A Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products (particularly decision trees #6 and #8), which will identify the data that need to be submitted for products with or without preservatives. Also refer to USP <61> <62> <1111> for microbial limits testing methods and the expected limits for aqueous preparations for oral use.

**Pharmacology / Toxicology Discussion:**

There are substantial published preclinical studies on sulfates. Furthermore, the WHO Food Additives Committee reviewed the published studies on sodium sulfate and concluded that the results did not raise a concern about its safety. In addition, there is extensive literature on the use of magnesium sulfate as a tocolytic agent. As a result, Braintree Laboratories, Inc submits that no additional preclinical or pharmacokinetic studies are warranted for this IND or for eventual NDA approval.

- 1) Does FDA agree?

**Response: No, we do not agree. The dose of sodium sulfate as a food additive is much lower than that of Oral Sulfate Solution.**

- 2) Are any additional toxicology studies needed?

**Response: You need to conduct 4-week oral toxicity studies in a rodent and a nonrodent species with your formulation.**

- 3) Are any additional pharmacokinetic studies needed?

**Response: No. We do not recommend any pharmacokinetic studies with your formulation.**

**Clinical Studies-Phase 1 & 2:**

The Phase 1 & 2 studies completed demonstrate the contribution of each ingredient and the necessary dose to effect stool removal and bowel cleansing. We believe that these studies satisfy FDA combination drug and dose-ranging requirements (ICH E4).

- 1) Does FDA agree?

**Response: Unfortunately, based upon the current data we are unable to answer your question at this time. However, the information you present, together with your phase 3 studies appear to be a logical way to address the combination rule, since we view your Oral Sulfate Solution as a combination drug.**

- 2) Are any other Phase 1 or 2 studies needed?

**Response: Given the characteristics of your solution, it will be important for you to describe the effect of your product in the face of hepatic and renal dysfunction. Please evaluate your product in geriatric subjects, those with hepatic impairment, and those with renal insufficiency.**

**Determine serum/plasma concentration profiles of electrolytes (sodium, potassium, magnesium and sulfate) and address the effect of renal impairment on the exposure of these electrolytes.**

**[ADDITIONAL COMMENTS: The sponsor asked if patients with renal impairment and with hepatic impairment could be evaluated as subgroups in phase 2 studies and if geriatric patients could be evaluated in phase 3 studies. The FDA responded that this was acceptable, but separate studies may be better. In response to the FDA's question, the sponsor stated that the phase 2 studies could be designed to have sufficient patients for an evaluation of the impact of hepatic impairment and renal impairment. The FDA suggested that the sponsor consult the following guidance documents available on the CDER website, "Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling" and "Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling". The sponsor proposed enrolling approximately 6 or 7 patients with renal impairment and 6 or 7 patients with hepatic impairment with matched normal controls per dose group. The FDA suggested using the formulation proposed for marketing.]**

**Clinical Studies-Phase 3:**

- 1) Two Phase 3 studies are proposed. A total of 360 subjects will be randomized to treatment with OSS. Is this adequate to demonstrate safety?

**Response: Recent safety reports indicated that phosphate preparations may cause renal failure in some patients post colonoscopy. These events were observed 1-6 months after colonoscopy. We recommend that all patients be followed up at 1, 3 and 6 month post colonoscopy to evaluate renal function.**

**[Additional Discussion: The FDA suggested that Braintree submit their proposed protocol change to provide for (b)(4) as the proposed comparator and request review and comment. In response to Braintree's question, the FDA stated that phase 2 data should be submitted and evaluated before the proposed phase 3 protocol could qualify for a special protocol assessment. The FDA explained that Braintree should try to show that their product is safer than phosphate products and monitor serum creatinine to assess renal function.]**

- 2) The two Phase 3 studies being proposed will use MoviPrep (b)(4) as active controls. Are these FDA-approved preps adequate for use as control groups?

**Response: Yes, these are acceptable comparators. However, one comparator could also be adequate from a regulatory perspective.**

**Please clarify whether you plan superiority studies or non-inferiority studies. If you proposed non-inferiority studies, please provide in the protocol the pre-specified statistical hypothesis and non-inferiority margin. The margin should be based on established efficacy data. (See statistical comments below.)**

**[Additional Discussion: In response to the sponsor's question, the FDA stated that GoLyteLy is an acceptable comparator.]**

- 3) Will these studies support OSS labeling for both administrations?

**Response: Both dosing regimens using in the studies appear acceptable. Final approval and label content are data dependent.**

- 4) Are the inclusion/ exclusion criteria for the proposed Phase 3 studies adequate to exclude patients that should not be enrolled for safety reasons?

**Response: There have been rare reports of generalized tonic-clonic seizures and/or loss of consciousness associated with use of sodium phosphate products in patients, so for your (b)(4) study we recommend exclusion of patients with a history of seizures and patients with a higher risk of seizure [i.e., those using concomitant medications that lower the seizure threshold (such as tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, or patients with known or suspected hyponatremia].**

The remainder of your eligibility criteria appears acceptable.

**[ADDITIONAL DISCUSSION: After discussion, the FDA stated that it is acceptable to include patients with a history of seizures and/or a higher risk of seizure, but these patients should be balanced in the placebo and active drug groups.]**

- 5) The primary efficacy variable is the same as that previously used for the NuLYTELY and HalfLYTELY pivotal studies. Is the proposed primary efficacy variable adequate to support approval of an OSS NDA?

**Response: Yes, this endpoint is acceptable.**

**Additional Statistical Comments on the Proposed Phase 3 Study Protocols:**

The statistical sections of each study protocol should include additional detail and specification with regard to the following: (Please refer to the ICH E9 guidance, *Statistical Principles for Clinical Trials*).

- a. Clarify whether your intention is to show superiority or non-inferiority over comparator products. State the statistical hypothesis to be tested (null and alternative) including clinical justifications for assumed effect size and/or non-inferiority margin.
- b. Clearly define both primary and secondary endpoints and analysis methods for each, including test statistics and/or confidence interval estimation procedures.
- c. Identify the primary and secondary analysis populations.
- d. Identify methods for handling any missing data or dropouts.
- e. Describe any secondary analysis methods such as those planned for analysis of center effects or other study factors.

**DECISIONS (AGREEMENTS) REACHED:**

None

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

1. Braintree will submit protocols for review. The study with (b) (4) as the comparator, will employ a non-inferiority design. The protocols will address the above statistical comments. They will include historical information to support the margin in the submissions.

**2. Braintree will conduct 4-week oral toxicity studies in rodent and non-rodent species.**

**ATTACHMENTS/HANDOUTS:**

None

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Brian Strongin  
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