



NDA 022372

NDA APPROVAL

Braintree Laboratories, Inc.
Vivian A. Caballero
Director, Regulatory Affairs
60 Columbian Street West
P.O. 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 (FDCA) for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution.

We acknowledge receipt of your submissions dated July 1, 2008; July 18, 2008; August 22, 2008; August 28, 2008; September 11, 2008; October 27, 2008; November 20, 2008; December 11, 2008; December 23, 2008; January 22, 2009; January 26, 2009, January 27, 2009; February 4, 2009; February 9, 2009; February 18, 2009; February 20, 2009; February 26, 2009; March 6, 2009; March 10, 2009; March 19, 2009, March 31, 2009; April 1, 2009; April 2, 2009; April 3, 2009; April 20, 2009; April 30, 2009; May 5, 2009; May 12, 2009; May 13, 2009; June 11, 2009; June 12, 2009; July 16, 2009; August 3, 2009; September 28, 2009; November 19, 2009; January 7, 2010; April 19, 2010; May 10, 2010; May 14, 2010; May 27, 2010; June 30, 2010; July 29, 2010; August 3, 2010; and August 5, 2010.

This new drug application provides for the use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) Oral Solution for cleansing of the colon in preparation for colonoscopy in adults.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and with the minor editorial revisions listed below.

Throughout the carton and container labels, revise the abbreviation “oz” to “ounce” or “ounces”, as appropriate.

We note that your August 5, 2010 submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert and Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, submitted July 29, 2010, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022372.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages birth to 16 years because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

1580-1: Conduct a retrospective study of colonoscopy rates in the pediatric population (birth through 16 years). This data review will determine the number of colonoscopies being performed in the pediatric population. The need to develop an age appropriate formulation will be based on the results of this study.

Final Protocol Submission:	November 30, 2010
Study Completion Date:	February 28, 2011
Final Report Submission:	May 31, 2011

1580-2: Conduct an open-label pilot study assessing the efficacy and tolerability of SUPREP in adolescents (12 years to 16 years). The adult formulation (and any age appropriate reformulations) will be evaluated for tolerability and efficacy in this pilot study.

Final Protocol Submission:	November 30, 2013
Study Completion Date:	August 31, 2014
Final Report Submission:	November 30, 2014

1580-3: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in adolescents (12 years to 16 years).

Final Protocol Submission:	February 28, 2015
Study Completion Date:	February 29, 2016
Final Report Submission:	May 31, 2016

1580-4: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in children (3 years to 11 years).

Final Protocol Submission:	August 31, 2016
Study Completion Date:	August 31, 2017
Final Report Submission:	November 30, 2017

1580-5: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in children (birth to 2 years).

Final Protocol Submission:	February 28, 2018
Study Completion Date:	February 28, 2019
Final Report Submission:	May 31, 2019

Submit all protocols to your IND 074808 and all final study reports to this NDA. Use the following designators, as appropriate, to prominently label all submissions:

Required Pediatric Protocol
Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of ischemic colitis, renal failure or other serious renal disease, seizure disorders, new arrhythmias, or other uncommon but serious adverse events. Available data for other drugs in the same pharmacologic class indicate the potential for these serious risks. Analysis of spontaneous postmarketing adverse events also will not be sufficient to assess the signals of serious risks of aggravation of gout and serious outcomes associated with elevations of creatine kinase related to the use of the drug.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1580-6: A prospective, descriptive epidemiologic study to identify adverse events associated with SUPREP administration in 20,000 patients undergoing screening colonoscopy and 20,000 patients in an appropriate control group. This study should be conducted in a data resource with access to electronic medical records (EMR); a claims-only database is insufficient. The eligible population will be all patients prescribed SUPREP. Outcomes of interest are those that occur within three months of SUPREP administration.

The timetable you submitted on December 16, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	November 30, 2010
Study Completion Date:	May 31, 2016
Final Report Submission:	November 30, 2016

Interim reports are to be submitted annually and crude exposure counts are to be submitted semiannually.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of dangerous fluid and electrolyte disturbances or renal injury, when available data for other drugs in the same pharmacologic class indicate the potential for a serious risk. Also, only a clinical trial will be sufficient to assess the signal of creatine kinase (CK) elevations related to the use of SUPREP.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1580-7: A randomized, active control, single-blind trial to evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUPREP prior to colonoscopy.

The timetable you submitted on December 16, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	November 30, 2010
Trial Completion Date:	November 30, 2012
Final Report Submission:	May 31, 2013

1580-8: A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking SUPREP.

The timetable you submitted on December 16, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	November 30, 2010
Trial Completion Date:	February 29, 2012
Final Report Submission:	August 31, 2012

Submit the protocols to your IND 074808, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required

will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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)). The details of the REMS requirements were outlined in our REMS notification letter dated June 22, 2010.

Your proposed REMS, submitted on July 29, 2010 and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to an evaluation of patients' understanding of the serious risks of SUPREP.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022372 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022372
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 022372
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22372

ORIG-1

BRAINTREE
LABORATORIES
INC

SUPREP BOWEL PREP KIT

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

/s/

DONNA J GRIEBEL

08/05/2010