021551_OriginalAppraal_Package.PDF

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Approval Package for:

APPLICATION NUMBER:
21-551

Trade Name:	HalfLytely and Bisacodyl Tablets Bowel Prep Kit
Generic Name:	Peg-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablets
Sponsor:	Braintree Laboratories, Inc.
Approval Date:	May 10, 2004
Indications:	Provides for the use of HalfLytely and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and biosacodyl tablets) for bowel cleansing prior to colonoscopy.

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APPLICATION NUMBER:

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EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative Document(s) and Correspondence	X

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APPLICATION NUMBER:

21-551

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-551

Braintree Laboratories, Inc.
Attention: Vivian Caballero
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

Dear Ms. Caballero:

Please refer to your new drug application (NDA) dated August 15, 2002, received August 16, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for HalfLytely® and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets).

We acknowledge receipt of your submission(s) dated September 23, October 24, November 25, 2002, January 28, February 10, April 14, May 12, May 19, June 3, June 4, June 10, November 6, 2003, and May 7, 2004.

The November 6, 2003 submission constituted a complete response to our June 16, 2003 action letter.

This new drug application provides for the use of HalfLytely® and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets) for bowel cleansing prior to colonoscopy.

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

Product Labels

1. Capitalized "PEG", increased the size and prominence of the generic name, and indicated the location of the lot number and expiration date on the HalfLyltely Bottle label and HalfLytely and Bisacodyl Tablets Bowel Prep Kit label.
2. Created two lines to separate the product and strength, added "Rx only" and directions on how to remove the tablets on the Biscodyl Delayed-Release Tablets label.
3. Created two lines to separate the product and strength, added "Rx only" on the Biscodyl Delayed-Release Tablets Blister card.

Package Insert

1. Capitalized "PEG" throughout insert.
2. Spelled out "Polyethylene glycol" under DESCRIPTION section.

3. Corrected spelling of "metabolite" and "methane" under CLINICAL PHARMACOLOGY section.
4. Added the following text to the ADVERSE REACTION section:

   "Published literature contains isolated reports of serious adverse reactions following the administration of (4L) PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss syndrome esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butterfly-like" infiltrate on chest X-ray after vomiting and aspirating PEG.

   In addition, during administration of 4L PEG-3350 bowel cleansing preparations the following serious adverse events were seen: two deaths in end-stage renal failure patients who developed diarrhea, vomiting, dysnatremia; tonic-clonic seizures in patients with and without prior history of seizures. These adverse events have not been reported in HalfLytely and Bisacodyl Tablets Bowel Prep Kit clinical trials."

The final printed labeling (FPL) must be identical to the enclosed labeling and the submitted labeling (package insert, bottle, box and blister label, and the blister card submitted May 7, 2004). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-551**." Approval of this submission by FDA is not required before the labeling is used.

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 are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitment in your submission dated May 7, 2004. This commitment is listed below.

1. Provide data regarding the degradation of bisacodyl in the acid stage and continue to develop an appropriate acid stage as a part of the complete dissolution method.

   Final Report Submission: Within 12 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 Tanya Clayton, Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Joyce Korvick
5/10/04 02:48:24 PM
for Dr. Robert Justice

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APPLICATION NUMBER:

21-551

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-551

Braintree Laboatories, Inc.
Attention: Vivian Caballero
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

Dear Ms. Caballero

Please refer to your new drug application (NDA) dated August 15, 2002, received August 16, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Half Lytely® Bowel Prep — PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets).

We acknowledge receipt of your submissions dated September 23, October 24, November 25, 2002, January 28, February 10, April 14, May 12, May 19, June 3, June 4, and June 10, 2003.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

Labeling

Submit draft labeling revised as indicated in the attached revised labeling for the package insert and component labels.

Clinical Pharmacology and Chemistry, Manufacturing and Controls

The rationale for choosing the conditions of the proposed *in-vitro* dissolution method are unclear. Data supporting the proposed conditions is needed before the method can be finalized. Therefore, please submit data supporting the dissolution method conditions. If the requested data is not available, please submit an acceptable *in-vitro* dissolution method.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Although not required for approval, please provide a response to our May 29, 2003 letter notifying you that the proposed tradename of Half Lytely Bowel Prep — was not acceptable.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

7 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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

/s/

Joyce Korvick
6/16/03 05:27:01 PM
for Dr. Robert Justice