CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 22-015
MiraLAX OTC
(Polyethylene Glycol 3350, NF Powder for Solution)
Braintree Laboratories, Inc.

The applicant makes the following submission of patent information in compliance with 21 CFR 314.53.

New Drug Application number: 22-015

Trade name: MiraLAX®

Active Ingredient: Polyethylene Glycol 3350, NF

Strengths of new drug: 17 grams once per day

Dosage form of new drug: oral powder for solution

United States patent number: 5,710,183, issued January 20, 1998, expiration date of July 14, 2015.

Patent owner: Braintree Laboratories, Inc., 60 Columbian Street West, Braintree, MA 02185-0929, vcaballero@braintreelabs.com

Name and address of agent authorized to receive notice of patent certifications: Robert Raleigh, General Counsel, Braintree Laboratories, Inc., 60 Columbian Street West, Braintree, MA 02185-0929, rraleigh@braintreelabs.com

This patent has not been submitted for this application, however it was submitted for NDA 20-698, the expiration date of the patent has not changed.

This patent is a method of use patent and claims the active drug substance that is the active ingredient in the drug product described in the application. The patent (5,710,183) claims (see claim 33) "*A method for improving bowel function in a mammal, comprising orally administering polyethylene glycol to the mammal, in an amount sufficient to improve bowel motility, stool formation, or both.*" It is the belief of the applicant that this method of use claim corresponds to the "Use" section of the proposed labeling contained in this application which states *"relieves occasional constipation"* and *"this product generally produces a bowel movement in 1 to 3 days"*.

To the knowledge of the applicant, other than the method of use patent described above (5,710,183), there are no relevant patents that claim the drug substance, drug product or method of use for the drug for which the applicant is seeking approval and with respect to which a claim of patent infringement could be reasonably asserted.

Vivian A. Caballero, Director, Regulatory Affairs

12-6-05
Date

EXCLUSIVITY SUMMARY

NDA # 22-015 SUPPL # HFD # 560

Trade Name MiraLAX

Generic Name polyethylene glycol 3350

Applicant Name Braintree Laboratories, Inc

Approval Date, If Known October 6, 2006

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.

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years under 314.108 (b)(4)(iv)

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# 20-698 Miralax

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).

NDA#

NDA#

NDA#

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:

Study 851-CR1 - Extended use of Miralax laxative in constipated patients

Study 851-ZCC - Miralax vs Zelnorm in treatment of patients with chronic constipation

Study 851-CR3 - An open label study of chronic miralax use in constipated patients

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.")

Investigation #1	YES ☐	NO ☒
Investigation #2	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?

Investigation #1	YES ☐	NO ☒
Investigation #2	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"):

Study 851-CR1 - Extended use of Miralax laxative in constipated patients

Study 851-ZCC - Miralax vs Zelnorm in treatment of patients with chronic constipation

Study 851-CR3 - An open label study of chronic miralax use in constipated patients

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		!
		!
IND # 28306	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 28306	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 ☐	! NO ☐
Explain:	! 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:

Name of person completing form: Keith Olin
Title: Regulatory Project Manager
Date: 10/31/06

Name of Office/Division Director signing form: Andrea Leonard-Segal, MD
Title: Director, Division of Nonprescription Clinical Evaluation

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

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

/s/

Andrea Segal
11/8/2006 03:40:16 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-015 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: December 8, 2006 **PDUFA Goal Date:** October 8, 2006

HFD____ **Trade and generic names/dosage form:** MiraLAX (polyethylene glycol 3350) powder for solution

Applicant: Braintree Laboratories, Inc **Therapeutic Class:** 8031200 LAXATIVES

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

X Yes. Please proceed to the next section.
No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Relief of occasional constipation (irregularity)

Is this an orphan indication?

☐ Yes. PREA does not apply. Skip to signature block.

X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo.__0__ yr.__0__ Tanner Stage_____
Max_____ kg_____ mo.__0__ yr.__16__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: The Sponsor is submitting a new pediatric formulation for use in birth to 16 years of age. This will be a new prescription NDA. The FDA will review the pediatric studies submitted to the prescription NDA and if they support the use of polyethylene glycol 3350 in pediatric ages birth to 16 years of age, then additional pediatric studies will be considered for OTC use.

Date studies are due (mm/dd/yy): 10/6/2016

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 22-015
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 6-23-2005)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 6-23-2005)

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

/s/

Keith Olin
10/6/2006 12:52:29 PM

NDA 22-015
MiraLAX OTC
(Polyethylene Glycol 3350, NF Powder for Solution)
Braintree Laboratories, Inc.

Debarment Certification:

Braintree Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Mark vB. Cleveland, Ph.D.

12/2/05
Date

Vice President, New Product Development
Braintree Laboratories, Inc.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

BRAINTREE LABORATORIES INC
Vivian Caballero
P.O Box 850929 60 Columbian Street West
Braintree MA 02185
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

2. TELEPHONE NUMBER
781-843-2202 221

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
polyethlyene glycol 3350, NF powder laxative (MiraLAX)

6. USER FEE I.D. NUMBER
PD3006332

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Vivian Caballero	Director, Regulatory Affairs	12/6/05

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PREA DEFERRAL GRANTED

NDA 22-015

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

Dear Ms. Caballero:

Please refer to your submission dated December 5, 2005, requesting a deferral of pediatric studies for MiraLAX (polyethylene glycol 3350) powder for solution.

We have reviewed the submission and agree that a deferral of pediatric studies in patients from birth to 16 years of age is justified for MiraLAX (polyethylene glycol 3350) powder for solution for relief of occasional constipation (irregularity) [redacted]

Accordingly, pediatric studies are deferred for your application under 505B(a) of the Federal Food, Drug, and Cosmetic Act until October 6, 2016.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of occasional constipation (irregularity) in pediatric patients from birth to 16 years of age.

Final Report Submission: October 6, 2016.

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

If you have any questions, call Keith Olin, Regulatory Project Manager, at 301-796-0962.

Sincerely

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Andrea Segal
10/6/2006 02:43:32 PM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: 06/19/2006 **DATE OF DOCUMENT:** 12/06/2005	**DESIRED COMPLETION DATE:** 08/30/2006 **PDUFA DATE:** 10/08/2006	**OSE REVIEW #:** 06-0192

TO: Andrea Leonard-Segal, M.D.
Acting Director, Division of Nonprescription Clinical Evaluation
HFD-560

THROUGH: Alina R. Mahmud, R.Ph., MS, Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Jinhee L. Jahng, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **MiraLAX™** (Polyethylene Glycol 3350, Powder Laxative) **NDA #:** 22-015	**SPONSOR:** Braintree Laboratories, Inc

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, MiraLAX. However, we are concerned with having two products with identical product characteristics in both the prescription (Rx) and OTC markets. Keeping the Rx version of MiraLAX on the market while launching an OTC version of MiraLAX may introduce confusion for healthcare practitioners who may not know which one to prescribe/dispense. Thus we recommend the prescription product be discontinued once the Rx to OTC switch is approved. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before the NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

2. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC does not provide comments on the promotional aspects of over-the-counter (OTC) products. The Federal Trade Commission (FTC) regulates the advertising of OTC products.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND PACKAGING REVIEW

DATE OF REVIEW: July 10, 2006

NDA#: 22-015

NAME OF DRUG: MiraLAX (Polyethylene Glycol 3350 Powder Laxative)

NDA HOLDER: Braintree Laboratories, Inc

I. INTRODUCTION:

This consult was written in response to a request from the Division of Nonprescription Clinical Evaluation (HFD-560), for assessment of the proprietary name, "MiraLAX", regarding potential name confusion with other proprietary or established drug names. MiraLAX is the proposed proprietary name for an over-the-counter (OTC) laxative containing the active ingredient, polyethylene glycol 3350.

Currently, this active ingredient is available as a prescription product with the same strength and dose under the same proprietary name, MiraLAX. According to the Division's project manager, the sponsor plans on marketing both the prescription version and the OTC MiraLAX at the same time, utilizing the same name. The sponsor also plans on submitting an application for a new pediatric indication as a prescription only product and introducing a new dosage form. Container labels and carton labeling were provided for review and comment.

PRODUCT INFORMATION

MiraLAX (Polyethylene Glycol) is an osmotic agent which causes water to be retained with the stool. It is indicated for the relief of occasional constipation. The usual adult dose is 17 grams, completely dissolved in a 4 to 8 ounce beverage, drink once daily. MiraLAX will be available in a carton of 30 packets, each containing 17 grams of polyethylene glycol 3350 powder.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to MiraLAX to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name MiraLAX. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not provide comment on the promotional aspects of over-the-counter (OTC) products because the Federal Trade Commission (FTC) regulates the advertising of OTC products.

2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with MiraLAX. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

---

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

[4] Phonetic and Orthographic Computer Analysis (POCA)

[5] WWW location http://www.uspto.gov/tmdb/index.html.

[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s); Established name	Usual adult dose*	Other**
MiraLAX (OTC)	Polyethylene Glycol 3350 Powder	1 heaping tablespoon (17 grams) or fill to top of white section in cap, completely dissolve in 4 to 8 ounce beverage and drink once daily	
MiraLAX	Polyethylene Glycol 3350 Powder	1 heaping tablespoon (17 grams) or fill to top of white section in cap, completely dissolve in 4 to 8 ounce beverage and drink once daily	SA/LA
Mirapex	Pramipexole Tablets 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 1.5 mg	Initial treatment: Gradually increase dosages from a starting dose of 0.375 mg/day given in 3 divided doses, and do not increase more frequently than every 5 to 7 days. Maintenance treatment: Pramipexole tablets were effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day administered in equally divided doses 3 times/day with or without concomitant levodopa (approximately 800 mg/day).	SA/LA
Mycelex-7 (OTC) Mycelex-7 Combination Pack (OTC)	Clotrimazole Vaginal Cream, 1% Clotrimazole Vaginal Suppositories, 100 mg Clotrimazole Topical Cream, 1%	Insert 1 applicatorful per day, preferably at bedtime, for 7 consecutive days. Unwrap one insert, place it in the applicator, and use the applicator to place the insert high into the vagina, preferably at bedtime. Repeat this procedure daily for 7 consecutive days. For relief of external vulvar itching, squeeze a small amount of clotrimazole cream onto your finger and gently spread the cream onto the irritated area of the vulva. Use once or twice a day for up to 7 days as needed to relieve external vulvar itching.	SA/LA
Mycelex-3 (OTC)	Butoconazole nitrate Vaginal Cream, 2%	Insert 1 applicatorful of cream intravaginally for 3 consecutive days, preferably at bedtime.	
Mycelex (Rx)	Clotrimazole Troches, 10 mg	1 troche slowly dissolved in the mouth, 5 times a day for 14 consecutive days. For prophylaxis to reduce the incidence of orapharyngeal candidiasis in patients immunocompromised, the recommended dose is one troche three times daily for the duration of chemotherapy or until steroids are reduced to maintenance levels.	

*Frequently used, not-all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

MiraLAX has been marketed since February 18, 1999. Thus, DMETS searched the FDA Adverse Events Reporting System (AERS) database to determine any post-marketing safety reports of medication errors associated with MiraLAX. The MedDRA High Level Group Term (HLGT) "Medication Error", tradename and verbatim "MiraLa%" were used to perform the searches. In a consult reviewed on May 9, 2006 (OSE Consult #06-0113), five cases involved confusion between Mirapex and MiraLAX. This search did not produce any new cases. In OSE Consult #06-0113, DMETS attributed the medication errors to a lack of familiarity with the introduction of MiraLAX and name recognition of the existing product, Mirapex. Oftentimes, medication errors involving name confusion occur during the initial launch phase of a new product into the marketplace. However, DMETS believes that due to the current name recognition of MiraLAX, the potential for further name confusion involving Mirapex has been decreased.

C. SAFETY EVALUATOR-RISK ASSESSMENT

In reviewing the proprietary name MiraLAX, the primary concerns relating to look-alike and sound-alike confusion with MiraLAX are MiraLAX (Rx), Mirapex, and the OTC and Rx Mycelex products. Upon initial review of MiraLAX(Rx), Mirapex, and Mycelex (Rx and OTC), DMETS does not believe that these names will be a source of error with MiraLAX, particularly since no recent errors relating to the labels and labeling of these products and MiraLAX were reported and the OTC version of MiraLAX has identical product characteristics to the Rx product. Additionally, we do not believe that the introduction of MiraLAX as an OTC product will increase the occurrence of errors. In particular, the OTC Mycelex varies from MiraLAX (OTC) in dosage form (vaginal cream or suppository) and route of administration (vaginal vs. oral). And since OTC products are typically arranged by therapeutic class, the likelihood that MiraLAX and Mycelex will be adjacent to each other in the pharmacy is minimal. We will therefore not review the aforementioned names.

DMETS notes that the product characteristics of the Rx version of MiraLAX and the OTC version of MiraLAX are identical. We have concerns that if a prescription and OTC version with identical product characteristics co-exist in the marketplace, prescribers might not know which product to dispense. Products which co-exist in both marketplaces typically vary with respect to strength – the OTC version usually has a lesser strength (ex. Zantac, Motrin, Prilosec). In the case of MiraLAX, since no differences exist, DMETS questions the justification for marketing an OTC version in conjunction with the Rx version. In this case, we would suggest discontinuing the Rx version at the launch of the OTC version of MiraLAX.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and carton labeling of MiraLAX, DMETS has attempted to focus on safety issues relating to medication errors. DMETS has identified the following areas of improvement, which might minimize potential user error.

A. GENERAL COMMENT

1. The statement "Prescription Drug Strength" is too prominent and diverts one

attention away from the proprietary and established names. Decrease the prominence of this statement on the labels and labeling.

2. Ensure that the "NEW" statement on the principal display panel appears for a period not to exceed six months.

3. DMETS questions if there is data to support the label and labeling comment that MiraLAX is "non-habit forming". If it is for occasional use, how would it become habit forming?

B. CONTAINER LABEL

See comments A1 - A3

C. CARTON LABELING

1. See comments A1 - A3.

2. The size of the company's name on the top flap and side panels competes with the proprietary and established names on the side panels. Decrease the size of the company name so that it is less prominent.

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/s/

Denise Toyer
9/13/2006 07:56:45 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/13/2006 10:38:19 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: August 17, 2006

TO: Vivian Cabellero, Director of Regulatory Affairs
Braintree Laboratories, Inc

FROM: Keith Olin, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

SUBJECT: **Email Correspondence to Braintree Labs: Clarification of request for 120 Safety Report and medwatch forms**

NDA 22-015, MiraLAX

Vivian,

Please Include the following in the safety update:

1. Any new postmarketing adverse reports
   - deaths
   - serious adverse events
   - others

   Include the individual MedWatch forms.

   For deaths and serious adverse events, a narrative description, similar to that provided for cases submitted in the NDA, should be included.

   Provide a tabular listing of all new postmarketing adverse reports (from where the data left off in the NDA up until the present time). Also provide a tabular listing that totals all postmarketing adverse events from 1999 until present and provide this in a separate table.

2. Any new published or available unpublished studies relevant to the use of PEG for the treatment of constipation (whether acute or chronic)

3. Information on marketing of PEG for treatment of constipation in other countries. Distinguish between information from countries where the product is marketed by prescription and where it is marketed over-the-counter or behind-the-counter.

4. Foreign labeling if marketed in other countries over-the-counter for treatment of constipation.

Medwatch Forms Clarification:

5. Send copies of all 125 Medwatch forms. The reviewer would like to know:
   What kind of allergic reactions occurred?
   Were there other medications involved that may have been primarily responsible?
   If possible , please to put together a table that provides age, medical conditions, concomitant medications and a brief narrative description of the event.

Since you recently sent in updated information about overdose and abuse, no additional information is needed unless there is newly available published data

If you have any questions, please contact me.
LCDR Keith Olin
301-796-0962
Keith.Olin@fda.hhs.gov

From: Caballero, Vivian [mailto:VCaballero@braintreelabs.com]
Sent: Monday, August 14, 2006 2:39 PM
To: Olin, Keith
Subject: RE: NDA 22-015 MiraLAX
Keith,

Can you please provide additional clarification for this request?

NDA 22-015, Module 5, Volume 11.1, Tab 5.3.6 summarizes, by body systems, all AEs received since approval of the MiraLAX Rx NDA (NDA 20-698, February 18, 1999).

Is the Medical Reviewer asking for copies of all 125+ AEs?

Thank you,

Vivian

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/s/

Keith Olin
8/17/2006 09:27:50 AM
CSO

From: Olin, Keith [mailto:keith.olin@fda.hhs.gov]
Sent: Thursday, August 10, 2006 4:30 PM
To: Caballero, Vivian
Cc: Olin, Keith
Subject: NDA 22-015 MiraLAX

Vivian,
As per conversation, please provide the following:
1) Provide the Medwatch forms on all postmarketing adverse events they mention in NDA.
Thanks,

LCDR Keith Olin

August 14, 2006
Re.: 120-day safety update

Good afternoon Keith,

It does not appear that a 120-day safety update has been submitted. I was reviewing the regulations and 314.50(d)(5)(vi)(b) states that "Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content."

Can you please provide guidance on the form and content that the reviewers would like for this update?

Thank you,

Vivian

Vivian A. Caballero
Director, Regulatory Affairs
BRAINTREE LABORATORIES, INC.
(781) 843-2202 ext. 221

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

EMAIL TRANSMITTAL SHEET

DATE: June 27, 2006

To: Vivian A. Caballero Director, Regulatory Affairs	**From:** Keith Olin, R.Ph. Regulatory Project Manager
Company: Braintree Laboratories, INC	Division of nonprescription Clinical Evaluation
Email Address:	**Fax number:** (301)796-9899
Phone number: 781-843-2202	**Phone number:** (301) 796-0962

Subject: NDA 22-015 – information request

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Vivian,

Here is another request for NDA 22-015:

For the comprehensive safety review of NDA 22-015, please submit the following information:

1) Provide a tabular listing of all subjects with two or more consecutive abnormal lab values. Please group by study, by subject number, and by treatment group. In addition, please include normal range, baseline lab value, abnormal lab value with correlating visit number.

2) Provide information on subjects using narrow therapeutic index drugs. Did any of these subjects require changes in dose of the narrow therapeutic index medication or experience any abnormal drug levels during the studies?

3) Address any documented use of Miralax with individual eating disorders.

If you have any question, please let me know.

LCDR Keith Olin
301-796-0962
Keith.Olin@fda.hhs.gov

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/s/

Keith Olin
8/14/2006 10:58:01 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Grace Carmouze, Lead Project Management Officer
Pediatric and Maternal Health Staff
Office of New Drugs

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Keith Olin, RPM
Division of Nonprescription Clinical Evaluation (DNCE)
Office on Nonprescription Products
301-796-0962

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
08/7/06		22-015	N	12/06/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
MiraLAX	High		09/20/06

NAME OF FIRM: Braintree Laboratories, Inc

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Braintree Laboratories has submitted an new NDA for an Rx to OTC switch for MiraLAX (polyethylene Glycol 3350) powder. MiraLAX is a laxative used for the treatment of occassional constipation. Miralax claims that it will produce a bowel movement in 1 to 3 days. The original NDA submission (December 6, 2005), Braintree Labs requested a deferral for the pedriatric ages groups birth to 16 years. Please advise DNCE on whether Miralax should be used in the pediatric population under the age of 16 as an over-the-counter product and if so, what studies should we include in the PMC. The PDUFA goal date for this NDA is October 8, 2006.

SIGNATURE OF REQUESTOR
Keith Olin, Regulatory Project Manager

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

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/s/

Keith Olin
8/8/2006 02:48:03 PM

MEMORANDUM

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

DATE: July 28, 2006

TO: Vivian Caballero
Director, Regulatory Affairs
Braintree Laboratories

FROM: Keith Olin, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

SUBJECT: **Information Request**
NDA 22-015, MiraLAX

Vivian,

Here is the request that I spoke to you about:

1) Provide a tabular listing of all study subjects in studies 851-CR1 and 851-CR3 who had their dose of Miralax reduced during the course of the study. Subjects should be listed by study, site, and subject number. The table should include information on each subject's age, gender, medical history, concomitant medications, inciting adverse event and study day(s) of occurrence, treatment needed other than dose reduction, and outcome. Include the reduced dose of Miralax and whether the dose needed to be adjusted more than once.

If you have any questions, please let me know.

LCDR Keith Olin
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
301-796-0962
Keith.Olin@fda.hhs.gov

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/s/

Keith Olin
7/28/2006 12:09:29 PM
CSO

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 12, 2006

TO: Keith Olin, Regulatory Project Manager
Karen Feibus, M.D., Clinical Reviewer
Division of Non-Prescription Clinical Evaluation

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

FROM: Andrea Slavin, RN
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-015

APPLICANT: Braintree Laboratories, Inc.

DRUG: MiraLax® (polyethylene glycol 3350 powder for solution)

THERAPEUTIC CLASSIFICATION: Rx-to-OTC switch, standard review

INDICATION: Treatment of occasional constipation

CONSULTATION REQUEST DATE: January 26, 2006

DIVISION ACTION GOAL DATE: October 6, 2006

PDUFA DATE: October 8, 2006

I. BACKGROUND:

MiraLax® (polyethylene glycol 3350 powder for solution) was approved as a prescription drug for the treatment of occasional constipation on February 18, 1999. The sponsor is now proposing a switch from prescription to over-the-counter (OTC) status. MiraLax® will be the first in its class OTC drug for the treatment of constipation.

The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The sites were selected by the medical officer in the Division of Gastroenterology Products.

2. Lawrence Wruble, M.D. (site #149)
Memphis Gastroenterology Group
80 Humphreys Center, Suite 220
Memphis, TN 38120

a. What was inspected: All 14 randomized subjects' records were audited for data integrity.

b. Limitations of Inspection: None.

c. General Observations/Commentary: No significant deviations from FDA regulations were observed.

d. Data from this site are acceptable.

B. Protocol #851-ZCC

1. Robert Bargar, M.D. (site #151)
Boston Clinical Trials
18 Shepard Street
Brighton, MA 02135

a. What was inspected: Of 32 randomized subjects, 16 subjects' records were audited for data integrity.

b. Limitations of Inspection: None.

c. General Observations/Commentary: Significant findings: Subject 003 was not listed on the sponsor's data listing of subjects who discontinued the study. Missed calls to the IVRS system are underreported on the sponsor's protocol violations data listing.

d. Data from this site are acceptable.

2. Dennis Riff, M.D. (site #141)
Advanced Clinical Research Institute
1211 West La Palma Avenue, Suite 602
Anaheim, CA 92801

a. What was inspected: All 24 randomized subjects' records were audited for data integrity.

b. Limitations of Inspection: None.

c. General Observations/Commentary: No significant deviations from FDA regulations were observed.

d. Data from this site are acceptable.

The following 2 clinical studies were audited:

#851-CR1: "Extended Use of MiraLax® Laxative in Constipated Patients"

The primary efficacy endpoint for #851-CR1: overall treatment success defined as a 0.50 or greater rate of successful treatment weeks. A successful treatment week is defined as ≥ 3 satisfactory bowel movements with 1 or fewer additional ROME criteria without the aid of rescue medication or prohibited laxatives. A successful treatment week rate is defined as the ratio of successful treatment weeks to total number of weeks of actual treatment.

#851-ZCC: "MiraLax™ vs Zelnorm™ in Treatment of Patients with Chronic Constipation"

The primary efficacy endpoint for #851-ZCC: overall treatment success defined as a 0.50 or greater rate of successful treatment weeks. A successful treatment week is defined as ≥ 3 satisfactory bowel movements with 1 or fewer additional ROME criteria without the aid of prohibited laxatives. A successful treatment week rate is defined as the ratio of successful treatment weeks to total number of weeks of actual treatment.

Summary Report of Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Charles Barish, MD/#102	Raleigh, NC	851-CR1	4/3/0/6 – 4/6/06	4/24/06	VAI
Lawrence Wruble, MD/#149	Memphis, TN	851-CR1	2/28/06 – 3/1/06	3/20/06	NAI
Robert Bargar, MD/#151	Brighton, MA	851-ZCC	3/31/06 – 4/7/06	4/18/06	NAI
Dennis Riff, MD/#141	Anaheim, CA	851-ZCC	2/27/06 – 3/7/06	5/25/06	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #851-CR1

1. Charles F. Barish, M.D. (site #102)
   Wake Research Associates, LLC
   3100 Blue Ridge Road, Suite 200
   Raleigh, NC 27612

a. What was inspected: All 15 randomized subjects' records were audited for data integrity.

b. Limitations of inspection: None.

c. General observations/commentary: Significant findings: For 10 of 15 subjects, there was a discrepancy between drug return forms and drug accountability logs. The investigator submitted a written response to Form FDA 483 promising corrective actions. The response is acceptable.

d. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, at Dr. Barish's site, there was an observation pertaining to documentation of drug accountability; at Dr. Bargar's site, one subject (003) was not listed on the sponsor's data listing of discontinued subjects and not all missed calls to the IVRS were listed on the sponsor's data listing of protocol violations; at Dr. Riff's site and Dr. Wruble's site, no significant deviations from FDA regulations were observed.

Data from all 4 sites are acceptable in support of NDA 22-015.

{See appended electronic signature page}

Andrea Slavin, RN
Consumer Safety Officer

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

Andrea Slavin
7/21/2006 09:56:14 AM
CSO

Constance Lewin
7/21/2006 02:23:26 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: July 14, 2006

TO (via email): Vivian A. Caballero
Director, Regulatory Affairs
Braintree Laboratories, Inc

FROM: Keith Olin
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

SUBJECT: **Medical Officer request for information**
NDA 22-015, MiraLAX

Vivian,

The medical officer is requesting the following information to help with the review of NDA 22-015.

Submit or clarify the following information:

1) A study summary reports from studies 851-3 and 851-6 that were submitted to NDA 20-698 and include all tabular appendices that address safety.

2) In the study report for Protocol 851-CR3, section 9.3 describes the exclusion criteria. It states: patients who met any of the following criteria were excluded from the study: (6) loose stools are not present, and there is insufficient criteria for IBS.
Clarify the meaning of this statement "patients who met any of the following criteria were excluded from the study: (6) loose stools are not present, and there is insufficient criteria for IBS."

Please let me know if you have any questions.

LCDR Keith Olin
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
301-796-0962
Keith.Olin@fda.hhs.gov

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/s/

Keith Olin
7/14/2006 04:06:05 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-015

INFORMATION REQUEST LETTER

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

Dear Ms. Caballero:

Please refer to your December 6, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Miralax OTC (polyethylene glycol 3355) oral powder.

We are reviewing the statistical 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.

Provide the following information for the two Studies 851-CR1 and 851-ZCC:

1. For each of the two Studies 851-CR1 and 851-ZCC, please provide data in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations.* It is suggested that the following variables be included:

   Study number;
   Investigator or Center code;
   Region;
   Patient discounted (yes or no);
   Patient number/name;
   Treatment name (MiraLax or Placebo);
   Intent-to-treat (ITT) population (yes or no);
   Per-protocol (PP) population (yes or no);
   Gender;
   Age;
   Race;
   Weight;
   Treatment weeks;
   Primary efficacy endpoint: overall treatment success (yes for responder or no for non-responder);
   Number of successful weeks assessed by primary definition;
   Successful treatment week rate;
   Number of successful weeks assessed by ROME;

Number of successful weeks assessed by supper efficacy;
Number of successful weeks assessed by ROME#1;
Number of successful weeks assessed by ROME#2;
Number of successful weeks assessed by ROME#3;
Number of successful weeks assessed by ROME#4;
Total number of bowel movements (BM) per week;
Satisfactory bowel movements (BM) per week;
Complete spontaneous BM, without aid of rescue medication, per week;
Number of weeks that patients indicated that they had adequate relief;
Number of tablets of rescue medication use per week.

To the data set described above, add additional variables needed (but not included in the above list) for the above analyses. Also modify the programs to be able to input data from the data set described in section 1.

2. Provide the statistical efficacy analysis programs for the primary and secondary efficacy endpoints described in the sections 9.7.1 to generate the results presented in section 11.4 in volumes 8.1 and 9.1 for both studies 851-CR1 and 851-ZCC.

If you have any questions, call LCDR Keith Olin, Regulatory Project Manager, at 301-796-0962.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
4/27/2006 11:26:46 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-015

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

Dear Ms. Caballero:

Please refer to your December 6, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MiraLAX OTC (polyethylene glycol 3350) powder.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 6, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. A statement regarding facilities' readiness for GMP inspection was not submitted.

2. The summary of safety information is incomplete.

3. Annotated specifications for the label and labeling were not submitted.

4. The patent information is incomplete.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

1. A statement regarding facilities' readiness for GMP inspection.

2. A tabulated comparison outlining all CMC differences between this NDA and NDA 20-698.

3. Information for safety and usage about where Miralax is marketed (RX or OTC) in other countries.

4. Tabular data on abnormal electrolyte (Na, K, Cl, HCO3, Ca, and Mg) and creatinine levels for study participants. Normal reference ranges for these laboratories, the incidence of abnormal values, any associated adverse experience, corrective actions, and individual listings should be provided. These results are too grouped and presented by laboratory test and include patient ID numbers.

5. A summary of the adverse event data, in tabular form, from the 31 published literature articles submitted with the NDA.

6. Annotated specifications for the label and labeling.

7. Augment the submitted information on Miralax overdose and abuse potential with data from sources such as the US poison control centers, Drug Abuse Network, and international safety database.

8. Patent information on form FDA 3541a.

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.

If you have any questions, call LCDR Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
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