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moral

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark Cleveland, Ph.D.
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

FEB 19 1998

Dear Dr. Cleveland:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Miralax[®] (polyethylene glycol 3350, NF) for Oral Solution.

We also refer to the meeting between representatives of your firm and FDA on July 9, 1997. The following represents our summary of the meeting.

MEMORANDUM OF MEETING MINUTES

- Meeting Date:** July 9, 1997
- Time:** 10 AM-12 PM
- Location:** WOC2, Room 6027 Conference Room
- Application:** NDA 20-698; Miralax (Polyethylene Glycol [PEG] 3350 NF) Powder for Oral Solution
- Type of Meeting:** Further Discussion of February 24, 1997 Not Approvable Letter
- Meeting Chair:** Dr. Murray Lumpkin, Deputy Center Director (Review Management)
- Meeting Recorder:** Ms. Melodi McNeil, Regulatory Health Project Manger
- FDA Attendees, titles, and Office/Division:**

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

- Dr. Lilia Talarico, Acting Division Director
- Ms. Kati Johnson, Supervisory Consumer Safety Officer
- Ms. Melodi McNeil, Regulatory Health Project Manager

Office of Drug Evaluation III (HFD-103)

- Dr. Paula Botstein, Acting Office Director

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Office of the Center Director (HFD-002)

Dr. Murray Lumpkin, Deputy Center Director (Review Management)

External Constituent Attendees and titles:

Braintree Laboratories, Inc.

Ms. Vivian Caballero, Director, Regulatory Affairs
Dr. Mark Cleveland, Vice-President, New Product Development
Dr. Jack DiPalma, Investigator
Dr. Wayne Pierson, Statistician
Mr. Harry Keegan, President

Background: NDA 20-698 was submitted on February 26, 1996 to market Miralax (PEG 3350, NF) Powder for Oral Solution, at a dose of 17 gm, for the treatment of occasional constipation. The following studies were submitted in support of approval:

1. **851-3**, considered pivotal by the firm, was a single center crossover study which randomized 50 constipated patients, defined as those with ≤ 3 bowel movements per week and/or ≤ 300 gm of stool per week, to a first period (10 days) of either 17 or 34 gm of PEG therapy. Subsequently, without a washout interval, subjects were randomized to second or third periods of placebo (PBO) or the alternate PEG dose.
2. **851-4** was a nursing home study identical in design to Study **851-3**. Four of the first five patients treated with either 17 or 34 gm of PEG experienced diarrhea, therefore, PEG doses were reduced to 6 and 12 gm for the remaining 30 patients.
3. **851-5** was a single-center crossover study in which 25 patients were randomized to PEG 17 gm or PBO.
4. **851-6**, considered pivotal by the firm, was a parallel study which enrolled 151 subjects who were randomized to PBO or PEG 17 gm.

In a February 24, 1997 Not Approvable letter the firm was informed that while Study **851-6** provided support for the 17 gm dose of PEG, Study **851-3** was insufficient to support approval. The letter stated that an additional robust, adequate and well-controlled study would be necessary to demonstrate efficacy of the 17 gm dose. Further, in light of the diarrhea experienced by the elderly subjects who received 17 or 34 gm of PEG in Study **851-4**, the firm was requested to provide additional safety data on the proposed dose so that the drug's risks could be adequately characterized. A May 8, 1997 meeting, which included representatives

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from both the Division and the Office, was held at the firm's request. In this meeting the Agency reiterated the information in the Not Approvable letter and offered suggestions as to the design of a future clinical trial. Subsequently, on May 16, 1997 the firm requested a meeting with the Center's Deputy Director (Review Management) in a further attempt to resolve the differences of opinion that exist with regards to the safety and efficacy of this product. The firm has previously requested and received the clinical and statistical reviews of the application.

Note: The firm is also the sponsor of NDAs 19-011 (GoLYTELY, approved July 13, 1984) and 19-797 (NuLYTELY, approved April 22, 1991), comprised of PEG 3350 plus electrolytes (PEG-ELS) and indicated for one time use as bowel cleansing agents prior to colonoscopy.

Meeting Objectives:

1. To discuss the difference of opinion that exists between the Agency and the firm with regard to the safety and efficacy of this product
2. To review the currently available safety information for PEG

Discussion Points:

1. Dr. Cleveland emphasized that Miralax consists entirely of PEG 3350, NF and said no electrolytes are present in the formulation. [There had been some confusion about this point, and it was raised for clarification.]
2. Dr. Cleveland briefly summarized the compound's regulatory history. He indicated that drug development began in 1986 and added that the Phase I studies were designed with input from Dr. William Bacharach, a medical officer in the Division of Cardio-Renal Drug Products (from which the Division of Gastrointestinal and Coagulation Drug Products was created). According to the firm, Dr. Bacharach suggested that constipation be defined as "three or less bowel movements per week and/or 300 gm or less of stool per week," based on a chapter in Gastrointestinal Disease, by Drs. John S. Fordtran and Marvin H. Sleisenger. Subsequently, the firm met with the Agency on November 5, 1987 to design the Phase III studies, including 851-3. According to Dr. Cleveland, the Agency was aware that the firm intended to continue use of the Fordtran and Sleisenger definition of constipation as an inclusion criteria in Phase III. He also indicated that all design issues with Study 851-3 were resolved at the time of the November 1987 meeting and conveyed the firm's impression that the Agency was primarily concerned that Study 851-3 demonstrate a dose response. Note: No written documentation of the November 5, 1987 meeting is available, either from the firm or the Agency.

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The results of Study 851-3 were presented to the Agency in a subsequent meeting, held August 20, 1990. According to the firm, Dr. Stephen B. Fredd, former Division Director, suggested an additional Phase III study (851-6). He also identified several flaws in the design and execution of Study 851-3 and suggested *post hoc* analyses to compensate.

Agency representatives reminded the firm that Study 851-3's inclusion criteria of ≤ 3 bowel movements and/or ≤ 300 gm of stool per week does not correlate with the definition of constipation the Agency has consistently used (from the Federal Register tentative final OTC laxative monograph, published in 1985):

< 3 bowel movements per week. The firm was informed at a March 9, 1994 meeting with the Agency that this would be the criteria upon which the Agency would evaluate efficacy. (See attached minutes of March 9, 1994 meeting).

Dr. DiPalma added that the wide variety of definitions for constipation is indicative of the many schools of thought within the clinical community as to what constitutes this condition and said that none of the definitions apply in all cases, despite the fact that all are accurate. He estimated that of his patients who present with a chief complaint of constipation, only one in 20 would meet the Federal Register definition. Dr. Cleveland expressed the firm's concern that the statistical review of study 851-3 was overly focused on the inclusion criteria and suggested that because the OTC laxative monograph is not yet final, the proposed definition of constipation it contains can not be considered binding. Dr. Lumpkin questioned the clinical difference between the two definitions and suggested an internal Agency meeting with the GI physicians from HFD-180 to further explore this issue. He also offered the possibility of that a single member of the Agency's GI advisory committee could be consulted for advice, but emphasized that any discussions held with the full advisory committee would most likely not be able to be held in closed session as the subject is one of a public policy matter (definition of constipation).

It was the firm's position that the Agency used an unpaired t-test for analysis, when a paired test would have been more appropriate. (There was no FDA statistician present to confirm or refute this assertion, however, it can be included in the response to the Not Approvable letter for review). Dr. Cleveland reiterated the firm's position that Study 851-3 supports the efficacy of PEG 17 gm for the treatment of constipation and requested that it be analyzed according to the prospectively defined criteria.

3. According to the firm, the proposed dose of Miralax is 17 gm per day for two weeks, although Dr. Cleveland indicated that the drug is effective in the first week of therapy, provided it is taken as prescribed. In response to a question, the

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firm speculated that, if approved, Miralax would be used by non-nursing home patients who had failed traditional, short-acting laxatives, such as over the counter (OTC) preparations. Dr. Lumpkin questioned whether the patients in the clinical trials were representative of the population in which the firm thinks Miralax will be used. In response, Dr. Cleveland indicated that most subjects were dissatisfied with their current laxative therapy. According to the firm, there is no product currently available to treat this group of patients, but they estimated that 20% of purchased GoLYTELY and NuLYTELY is used off-label in small doses as a laxative. Dr. DiPalma stated that Miralax is not intended for chronic use, however, he was unable to estimate how many times in a year the "typical" patient might use it. In response to Dr. Botstein's question, he acknowledged that patients with idiopathic constipation may become constipated again within four to six months after a course of Miralax therapy.

4. A brief discussion was held about the effect of PEG doses other than 17 gm. Dr. Lumpkin commented that the firm had not undertaken a traditional dose-response study, however the doses (6 and 12 gm) in Study 851-4 appeared to be too low. Dr. DiPalma concurred that, although these doses worked for some subjects, overall they were ineffective. Dr. Lumpkin noted that PEG doses of 34 gm were associated with diarrhea. In response, Dr. Cleveland expressed the firm's belief that the diarrhea associated with this dose is evidence of the compound's "super efficacy." He said the diarrhea is not a safety problem because it is an expected consequence of laxative therapy, without associated morbidity.
5. The efficacy of PEG 17 gm was summarized. The Agency has already accepted Study 851-6 as supportive of efficacy. According to the firm, although 17 gm was an effective dose in Study 851-5 (when assessed overall), approximately half of the patients did not meet the protocol's definition of constipation. In Study 851-4, only a few patients received PEG 17 gm before the dose was decreased secondary to diarrhea.

Dr. DiPalma indicated that both subjective and objective efficacy assessments were made of PEG 17 gm at four points during Study 861-3 (at the end of the PBO run in and at the end of each treatment period). The firm said that the efficacy of PEG 17 gm from each treatment period was totaled to get an overall assessment of efficacy and reiterated their assertion that, when analyzed according to the protocol, Study 851-3 shows that dose to be effective.

Dr. Lumpkin emphasized that when designing a clinical trial, it is important to objectively define the disease state *a priori*, then evaluate whether patients can be said to have improved. In response, the firm commented that, although not

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presented in the NDA, they were able to show improvements in individual patient outcomes. Dr. Lumpkin noted that, given the crossover design of, the execution of, and the combined analysis of Study 851-3, the efficacy of the 17 gm dose was contaminated by that of the 34 gm dose. In response to a question from Dr. Lumpkin, the firm said that they had conducted a *post hoc* analysis, also not presented in the NDA, in which patients in the PBO run-in phase were compared to those at the end of the first treatment period, i.e. before they had been exposed to any other dose of Miralax, with "convincing" evidence of efficacy. Although this reanalysis does not include a concurrent control, rather, the patient is his/her own control, the firm was asked to submit it to the NDA, along with any other analyses which demonstrate the efficacy of PEG 17 gm.

When Dr. Talarico asked the firm to compare results from days one and seven of the PBO run in phase, then of days one and 10 of the first treatment period for both 17 and 34 gm, the firm said they would investigate the possibility but were not sure such an analysis was possible. Dr. Talarico requested that the reanalysis been done on a per patient basis, for "success" vs. "failure" as a binary endpoint using the protocol's definition of constipation (3 bowel movements per week). Other Agency representatives added that the analysis should be of the rate of constipation improvement from days one to seven (run in phase), versus days one to 10 (first treatment period). Dr. Lumpkin emphasized that statistical significance of any reanalysis would not necessarily ensure approval, because the clinical outcomes had to be clinically meaningful. Agency representatives also added that the user fee clock will not be re-started until all deficiencies in the Not Approvable letter are fully addressed. In response to a question, the firm indicated further clinical investigations to demonstrate efficacy (as requested in the Not Approvable letter) will be deferred until all other avenues for approval are exhausted.

6. Dr. Lumpkin commented that the safety database for Miralax is small and lacks information on elderly patients. He also questioned the firm about their plans to increase the database and said that the population of users defined in the labeling should be supported. He added that it is inappropriate to extrapolate safety information from PEG-ELS to PEG alone, given the differences in the way they are used (one time versus two weeks, respectively). The firm reiterated that PEG-ELS is sometimes used as a laxative, albeit off label, and said that safety was not a primary focus of the studies, given that PEG is widely used for other uses and is considered safe. They mentioned an open-label study of PEG with 50-75 subjects and estimated that approximately 250 patients have been exposed to Miralax thus far.

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Conclusions:

1. The Not Approvable action taken February 24, 1997 is still in effect.
2. It is the firm's position that they have made a scientifically valid case for the efficacy of PEG 17 gm.
3. It is the Agency's position that the design and execution of Study 851-3 make accurate interpretation of any results after the first treatment period extremely difficult. The firm was requested to conduct a number of reanalyses, including a comparison of results from the first treatment period to results from the placebo run-in phase, along with a summary of any available information to support the safety and efficacy of PEG 17 gm and submit these items to the NDA. The firm was informed that the User Fee clock will not be reactivated until each deficiency in the Not Approvable letter has been addressed.
4. Agency representatives commented that statistical significance of any reanalysis would not necessarily ensure approval, because the clinical outcomes must be clinically meaningful.
5. The Agency will hold an internal meeting to determine whether there is a significant clinical difference between the definition of constipation proposed in the Federal Register Tentative Final Monograph for OTC laxatives, published in 1985, and the one used as an inclusion criteria by the firm in Study 851-3.
6. The firm was informed of the possibility of seeking guidance from the Agency's gastrointestinal advisory committee, but apprised that if more than one committee member was consulted, the meeting would most likely not be able to be held in closed session as the subject is one of a public policy matter (definition of constipation).

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/s/ [redacted] 9/19/97

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

NDA 20-698
Page 8

APPEARS THIS WAY ON ORIGINAL

cc:

Original NDA 20-698
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-002/Lumpkin
HFD-180/Talarico
HFD-103/Botstein

Drafted by: mm/September 19, 1997/c:\wpfiles\csoln\20698709.adv

final: September 19, 1997 (rec'd signed copy of letter 2/18/98)

ISI 2/18/98

GENERAL CORRESPONDENCE (MINUTES SENT)

McNeil

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark Cleveland, Ph.D.
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

MAR 20 1997

Dear Dr. Cleveland:

Please refer to your new drug application for Miralax (polyethylene glycol 3350, NF) for Oral Solution.

We also refer to the March 14, 1997 telephone conversation between Ms. Vivian Caballero, Regulatory Affairs, of your firm and Ms. Melodi McNeil of this Division, in which you requested a copy of the Medical Officer's review of the application referenced above.

The review is enclosed for your convenience. We hope this information is helpful.

If you have any questions, please contact Melodi McNeil, Consumer Safety Officer, at (301) 443-0483.

Sincerely yours,

ISI [Redacted] *3/20/97*
3/10/97

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-698
HFD-180/Div. Files
Enclosed HFD-180/CSO/McNeil
HFD-180/Prizont

enclosed documents:

~~Medical Officer's Review~~ 19, 1997/c:\wpfiles\cso\20698703.gc

Initialed by: KJohnson 3/19/97

SFredd 3/20/97

final: March 20, 1997

GENERAL CORRESPONDENCE

McNeil

NDA 20-698

MAR - 7 1997

Braintree Laboratories, Inc.
Attention: Mark Cleveland, Ph.D.
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

Dear Dr. Cleveland:

Please refer to your new drug application for Miralax (polyethylene glycol ~~3350~~, NF) for Oral Solution.

We refer to our February 24, 1997 not approvable letter, in which we indicated that our analysis of pivotal study 851-3, a single center, double-blind, crossover study which randomized 51 constipated patients to 17 or 34 gm of polyethylene glycol (PEG) or placebo, following a seven day placebo run-in phase, showed no difference between PEG 17 or 34 gm and placebo ($p = 0.15$ and $p = 1.0$, respectively).

We also refer to the February 28, 1997 telephone conversation between Ms. Vivian Caballero, Regulatory Affairs, of your firm and Ms. Melodi McNeil, Consumer Safety Officer, of this Division, in which you requested a copy of the Clinical Statistical review for the application referenced above.

The review is enclosed for your convenience. We hope this information is helpful.

If you have any questions, please contact Melodi McNeil, Consumer Safety Officer, at (301) 443-0483.

Sincerely yours,

/s/  3/7/97
3/2/97

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

enclosure

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Page 2

enclosed documents:
Clinical Statistical Review
Addendum #1

cc:

Original NDA 20-698
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-720/Huque
HFD-720/AI-Osh

Drafted by: mm/March 6, 1997/c:\wpfiles\cso\n\20698703.gc

Initialed by: KJohnson 3/6/97

SFredd 3/6/97

final: March 7, 1997

GENERAL CORRESPONDENCE

APPEARS THIS WAY ON ORIGINAL

020
Merrill

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark Cleveland, Ph.D.
60 Columbian Street, P.O. Box 850929
Braintree, MA 02185-0929

JAN 29 1997

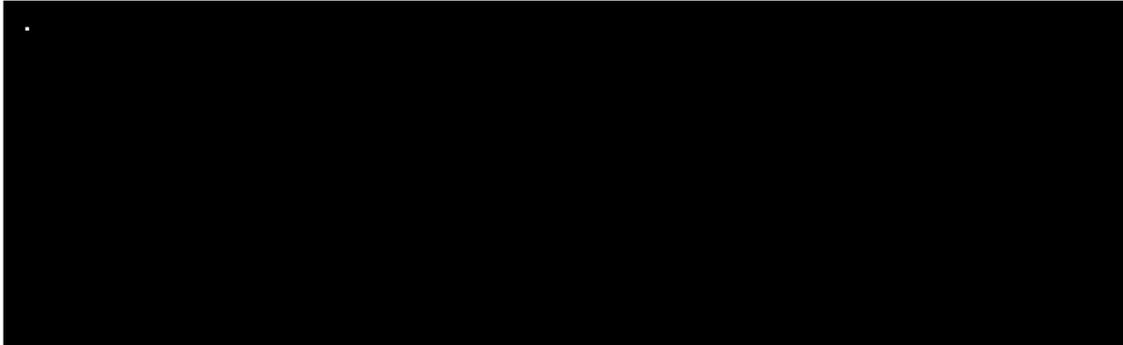
Dear Dr. Cleveland:

Please refer to your pending February 26, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Miralax (PEG 3350) for Oral Solution.

We also refer to your amendment dated May 16, 1996.

We have completed our review of the biopharmaceutics sections of your submissions and have the following comments and recommendations:

- a. While the draft labeling states that Miralax is not absorbed from the gastrointestinal tract, studies 851-2b and 851-2c showed that the PEG fecal recovery was incomplete and variable in constipated patients. We suggest that you conduct a multiple dosing study in constipated patients to show that PEG 3350 is not significantly absorbed and the absorbed PEG is not metabolized but excreted unchanged in the urine after multiple dosing. Consider using a different lavage technique to enable more complete recovery of nonabsorbed PEG.
- b. Please develop a sensitive, selective and reproducible [REDACTED] method capable of detecting PEG 3350 and its possible breakdown products in human plasma, urine and feces. [REDACTED]



We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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Page 2

If you have any questions, please contact Melodi McNeil, Consumer Safety Officer,
at (301) 443-0483.

Sincerely yours,

/s/ [Redacted]

1/29/97

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

- Original NDA 20-698
- HFD-180/Div. Files
- HFD-180/CSO/M.McNeil
- HFD-180/Duffy
- HFD-180/Frankewich
- HFD-870/Chen
- HFD-870/Kaus
- HFD-870/Choi

/s/ [Redacted]

1/29/97

Drafted by: mm/January 24, 1997/c:\wpfiles\cso\n\20698701.ir

Initialed by: SFredd 1/28/97

KJohnson 1/28/97

final: January 29, 1997

INFORMATION REQUEST (IR)

APPEARS THIS WAY ON ORIGINAL

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark Cleveland, Ph.D.
60 Columbian Street, P.O. Box 850929
Braintree, MA 02185-0929

APR 24 1996

Dear Dr. Cleveland:

Please refer to your pending February 26, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 851 (polyethylene glycol 3350, NF) Laxative.

We have conducted a preliminary review of your application and request the following information:

1. Biopharmaceutics:

- a. Please provide assay validation data for measuring [REDACTED] by [REDACTED]
- b. Please provide assay validation data for measuring [REDACTED]
- c. Because of the poor recovery of PEG 3350 noted in some subjects in the studies submitted in the NDA, please provide data which accounts for the disposition of PEG 3350.
- d. Please provide data which gives assurance of the [REDACTED] of the drug substance with [REDACTED] of any PEG 3350 which [REDACTED]

2. Statistics:

The following information should be submitted on a 3.5" diskette, in SAS 6.10 format, with a file extension of .sd2 for each of the clinical studies (851-3, 851-4, 851-5, and 851-6):

- a. Please provide all patient numbers, the investigators, and the centers where the studies took place.
- b. Please provide start and stop dates of treatment and doses, where applicable.
- c. Please specify whether or not patients completed the studies and their reasons for discontinuation, where applicable.

McNeil

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- d. Please provide efficacy parameters by study day, including frequency of bowel movements, stool weights, and patient and investigator subjective evaluations.
- e. Please provide baseline measurements for all efficacy parameters, in addition to demographic and laboratory data.

The following information should also be submitted on a 3.5" diskette, as described above, for study 851-6 only:

- a. The number, date, and results of the interim analysis which was conducted before the study ended.
 - b. The dates on which the patients entered the trial.
 - c. The dates of patient randomization and completion.
3. Chemistry, Manufacturing, and Controls: please provide specific DMF references which include either volume and page numbers, or submission dates.

We also request that you provide draft labeling for any applicable containers and/or cartons.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Melodi McNeil
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

/s/ [Redacted] 4-23-90
v/24/91

cc:

- Original NDA 20-698
- HFD-180/Div. Files
- HFD-180/CSO/M.McNeil
- HFD-180/RFrankewich
- HFD-180/JGibbs
- HFD-720/MHuque
- HFD-720/MAIOsh
- HFD-870/LKaus
- HFD-870/HRChoi

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

INFORMATION REQUEST

McNeil

NDA 20-698

Braintree Labs Inc.
Attention: Mark vB. Cleveland, Ph.D.
60 Columbian Street, P.O. Box 850929
Braintree, MA 02185-0929

MAR - 6 1996

Dear Dr. Cleveland:

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

Name of Drug Product: 851 (polyethylene glycol 3350, NF) Laxative

Therapeutic Classification: Standard

Date of Application: February 26, 1996

Date of Receipt: February 28, 1996

Our Reference Number: 20-698

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 28, 1996 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact me at (301) 443-0483.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

cc:
Original NDA 20-698
HFD-180/Div. Files
HFD-180/CSO/McNeil
HFD-180/MAdams
DISTRICT OFFICE

/s/ [Redacted] *3/6/96*

/s/ [Redacted] *3-6-96*

Melodi McNeil
Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

drafted: mm/March 5, 1996/c:\wpfiles\cso\n\20698603.ack
RD init:KJohnson 3/6/96
Final:March 6, 1996

ACKNOWLEDGEMENT (AC)

CSO/Kacuba

MEMORANDUM OF TELECON

DATE: December 11, 1998

APPLICATION NUMBER: NDA 20-698; Miralax (PEG 3350, NF) Powder for Oral Solution

BETWEEN:

Name: Dr. Mark Cleveland, Vice President, New Product Development
Ms. Vivian Caballero, Director, Regulatory Affairs
Phone: (781) 843-2202
Representing: Braintree Laboratories

AND

Name: Dr. Lilia Talarico, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Ms. Kati Johnson, SCSO
Ms. Alice Kacuba, CSO
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

BACKGROUND: NDA 20-698 was submitted on February 26, 1996 to market Miralax (PEG 3350) Powder for Oral Solution, at a dose of 17 gm, for the treatment of occasional constipation. A Not Approval (NA) letter was issued on February 24, 1997 informing the firm of clinical and chemistry deficiencies. Subsequently, meetings were held with representatives from the firm, the Division, and the Office to discuss the NA letter. On June 2, 1998, the firm submitted a complete response to the NA letter. An approvable (AE) letter was issued on December 3, 1998. (pending labeling and chemistry deficiencies.) On December 3, 1998, Dr. Cleveland and Ms. Caballero called me to discuss numerous issues regarding the labeling revisions that we requested in the December 3, 1998 AE letter. A telecon was scheduled to finalize the labeling. In preparation for this telecon, the firm faxed the proposed revisions to the Agency on December 9, 1998, and followed it up by submitting a hardcopy to the application (See attached).

TODAY'S PHONE CALL: The Agency addressed the firm's seven proposed revisions in the labeling.

1. The Agency accepted the firm's proposal to retain the statement "Patients taking other medications containing polyethylene glycol have occasionally developed urticaria suggestive of an allergic reaction" in the ADVERSE REACTIONS section of the package insert.
2. The Agency accepted the firm's proposal of moving the bolded colored line from under the word MiraLax to under the generic name in place of removing the line from the label.
3. The AE labeling removed the phrase "juice or other liquids" from the PRECAUTIONS, the DOSAGE AND ADMINISTRATION, and the HOW SUPPLIED sections of the package insert as well as from the "How to Take" section of the PATIENT INFORMATION label. Since the primary support for demonstration of efficacy was a study in which the drug was

taken with water, the firm's proposal to reintroduce the words "juice or other liquids" was not accepted.

4. The December 3, 1998 AE letter added a statement to the PRECAUTIONS.

DRAFT LABELING

[REDACTED]

This

revision was found acceptable.

5. The Agency accepted the firm's proposal to retain the statement "There is no evidence of tachyphlaxis" in the CLINICAL PHARMACOLOGY, "Pharmacology" section of the package insert.

6. The firm proposes that the "Geriatric Use" section read

DRAFT LABELING

[REDACTED]

7. The firm was directed to retain the wording proposed in the December 3, 1998 AE letter.

The firm agreed to submitting draft labeling incorporating these changes, along with addressing the chemistry deficiencies stated in the December 2, 1998 IR letter. The call was concluded.

./SI/

Alice Kacuba
Consumer Safety Officer

1-20-99

cc: Original

HFD-180/Div. File
HFD-180/L.Talarico
HFD-180/H.Gallo-Torres
HFD-180/A.Kacuba

APPEARS THIS WAY ON ORIGINAL

drafted: A.Kacuba/December 18, 1998

R/D initialed by: K.Johnson/January 9, 1999

final: AK/January 11, 1999

filename: c:\mydocuments\NDA20698-AE-labeling-questions-from-firm

TELECON

McNeil

MEMORANDUM OF TELECON

DATE: March 20, 1996

APPLICATION NUMBER: NDA 20-698; 851 (polyethylene glycol 3350, NF) Laxative

BETWEEN:

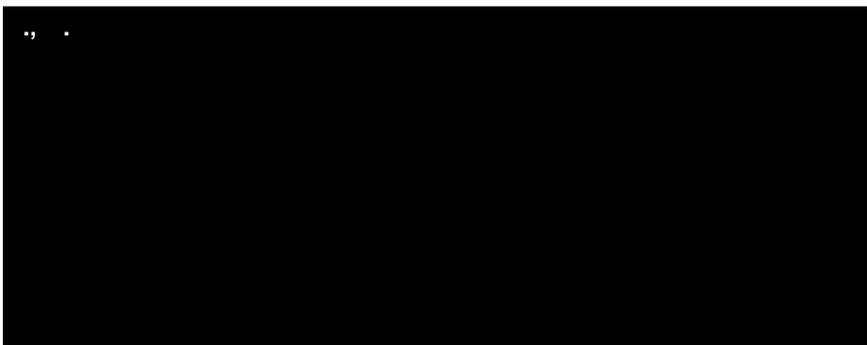
Name: Mark vB. Cleveland, Ph.D. and Ms. Vivian Caballero
Phone: (617) 843-2202
Representing: Braintree Laboratories, Inc.

AND

Name: Melodi McNeil, CSO
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Confirmation that manufacturing facilities are ready for inspection.

BACKGROUND: On February 26, 1996 the firm submitted a new drug application (NDA) for 851 (polyethylene glycol 3350, NF) Laxative. There are [redacted] manufacturing facilities listed in the NDA:



Per division policy, a phone call was made to confirm that each facility is ready for inspection.

TODAY'S PHONE CALL: Ms. Caballero confirmed that all facilities are ready for inspection. Dr. Cleveland noted that the [redacted] facility is not always open and advised the inspector to call before going to inspect it. The call was concluded.

HFD-180/Div. File
HFD-180/Melodi McNeil, CSO
HFD-180/RFrankewich
HFD-180/SFredd

/s/ [redacted] 4-2-96
Melodi McNeil, CSO
Consumer Safety Officer

RD init: KJohnson 4/2/96

TELECON

McNeil

MEMORANDUM OF TELECON

DATE: August 19, 1996

APPLICATION NUMBER: NDA 20-698; Miralax (851 Laxative, PEG 3350, NF)

BETWEEN:

Name: Mark vB. Cleveland, Ph.D.
Phone: (617) 843-2202
Representing: Braintree Laboratories, Inc.

AND

Name: Melodi McNeil, CSO
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Composition of Placebos used in clinical trials.

BACKGROUND: This application, submitted on February 26, 1996, provides for a 17 gram dose of Miralax to be reconstituted in 8 ounces of fluid and used for the treatment of occasional constipation. NDA 20-698 includes four placebo-controlled clinical trials (two pivotal) in support of approval. According to the submission, [redacted] was the placebo for studies 851-3, 851-4, and 851-5, and the placebo for study 851-6 was [redacted]. At the request of Drs. Duffy (Chemistry Team Leader), Frankewich (Reviewing Chemist), and Prizont (Reviewing Medical Officer), I called the firm to obtain more detailed information about the composition of the placebos used in the clinical trials.

TODAY'S PHONE CALL: In response to my questions, Dr. Cleveland replied that the [redacted] used in the studies was purchased from [redacted] and that he was unable to provide any qualitative/quantitative analysis as to its contents. In addition, he said the [redacted] was obtained from [redacted]. When I asked how much dextrose was used in each dose of placebo, Dr. Cleveland replied that the dosing scoop used to measure a 17 gm dose of the active drug was also used to measure the placebo, and, therefore, it was his position that patients received approximately 17 gm of [redacted]. I told Dr. Cleveland I would convey this information to the chemist and medical reviewers, and call him with any further questions. The call was concluded.

cc: Original NDA 20-698
HFD-180/Div. File
HFD-180/MMcNeil
HFD-180/EDuffy
HFD-180/RFrankewich
HFD-180/SFredd
HFD-180/RPrizont

/s/ [redacted] 8/21/96
Melodi McNeil, CSO
Consumer Safety Officer

TELECON

*McNeil***MEMORANDUM OF MEETING MINUTES**

Meeting Date: February 20, 1998

Location: 6B-45 (PKLN)

Application: NDA 20-698; Miralax (PEG 3350) Powder for Oral Solution

Type of Meeting: Discussion of February 24, 1997 Not Approvable Action

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Lilia Talarico, Division Director

Ms. Melodi McNeil, Regulatory Health Project Manager

Office of Drug Evaluation III (HFD-103)

Dr. Paula Botstein, Acting Office Director

Office of the Center Director (HFD-002)

Dr. Murray Lumpkin, Deputy Center Director (Review Management)

Background: NDA 20-698 was submitted on February 26, 1996 to market Miralax (PEG 3350, NF) Powder for Oral Solution, at a dose of 17 gm, for the treatment of occasional constipation. The following studies were submitted in support of approval:

1. **851-3**, considered pivotal by the firm, was a single center crossover study which randomized 50 constipated patients, defined as those with ≤ 3 bowel movements per week and/or ≤ 300 gm of stool per week, to a first period (10 days) of either 17 or 34 gm of PEG therapy. Subsequently, without a washout interval, subjects were randomized to second or third periods of placebo (PBO) or the alternate PEG dose.
2. **851-4** was a nursing home study identical in design to Study **851-3**. The protocol provided for enrollment of 50 constipated patients, randomized to either 17 or 34 gm of PEG. Four of the first five patients treated with either dose experienced diarrhea, therefore, PEG doses were reduced to 6 and 12 gm for the remaining 30 patients.
3. **851-5** was a single-center crossover study of one month's duration in which 25 patients were randomized to PEG 17 gm or PBO for a period of two weeks each.

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4. **851-6**, considered pivotal by the firm, was a parallel study which enrolled 151 subjects randomized to either PBO or PEG 17 gm.

In a February 24, 1997 Not Approvable letter the firm was informed that while Study **851-6** provided support for the 17 gm dose of PEG, Study **851-3** was insufficient to support approval. The letter stated that an additional robust, adequate and well-controlled study would be necessary to demonstrate efficacy of the 17 gm dose. Further, in light of the diarrhea experienced by the elderly subjects who received 17 or 34 gm of PEG in Study **851-4**, the firm was requested to provide additional safety data on the proposed dose so that the drug's risks could be adequately characterized. The firm has appealed the Not Approvable action to the Center levels. (For complete details of this application's regulatory history see the February 24, 1997 Not Approvable letter, Minutes of the May 8 and July 9, 1997 meetings with the firm, and Minutes of the December 17, 1997 internal meeting).

At a July 9, 1997 meeting which included representatives from the Division, Office and Center, the firm was requested to conduct a number of reanalyses of Study **851-3**, including a comparison of results from the first treatment period to results from the placebo run-in phase, along with a summary of any available information to support the safety and efficacy of PEG 17 gm and submit these items to the NDA. (Subsequently, Braintree provided several reanalyses of Study **851-3** in a submission dated July 21, 1997).

A December 17, 1997 internal meeting was held at Dr. Lumpkin's request to reassess the available clinical database for Study **851-3** and to reconsider whether it supports approval. To date, the Not Approvable action remains in effect.

Meeting Objective: To discuss the regulatory future of NDA 20-698

Discussion Points (bullet format):

1. Dr. Lumpkin summarized the outcomes of the July 9, 1997 meeting, specifically, that the firm was instructed to conduct several reanalyses of study **851-3** and that the Division was requested to reassess the available clinical database for the NDA.
2. The design, execution and results of Study **851-3** were summarized. Dr. Talarico highlighted the statistical deficiencies inherent in the firm's reanalysis, however, there was general agreement that a dose response effect was demonstrated, and that when the totality of evidence is considered, the Miralax 17 gm dose can be considered effective.
3. Based on the prolonged onset of action in the clinical trials (7 days in study **851-6**), numerous questions remain about (among other things) how Miralax would be

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labeled and used, the population for whom it is indicated, the conditions it would be used to treat, and what the recommended duration of treatment should be. Further, the diarrhea experienced by many subjects administered 34 gm of Miralax combined with the weak efficacy of the 17 gm dose suggest a compound with a narrow therapeutic range and are also cause for concern. It was decided that the firm will be asked to meet with representatives of the Division, Office, and Center, so they can be informed of the Agency's concerns and have an opportunity to respond to them.

Conclusion: Ms. McNeil will arrange a meeting between Agency representatives, as indicated above, and Braintree Laboratories.

Minutes Preparer: ^{/SI} [redacted] 2/23/98
Concurrence: ^{/SI} [redacted] 2-23-98

- cc: Original NDA 20-698
- HFD-180/Div. Files
- HFD-180/McNeil
- HFD-180/Prizont
- HFD-180/Talarico
- HFD-103/Botstein
- HFD-002/Lumpkin

Drafted by: mm/February 20, 1998/c:\wpfiles\cso\minutes\20698802.tea
Initialed by: LTalarico 2/23/98
final: February 23, 1998

MEETING MINUTES

APPEARS THIS WAY ON ORIGINAL