CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020698

MEDICAL REVIEW(S)

Kaczba

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-698
Sponsor:	Braintree Laboratories, Inc. AUG 26 1998
Date of Submission:	June 2, 1998
Drug:	MiraLax® (polyethylene glycol 3350, NF)
Pharmacological Category:	Laxative
Proposed Indication:	Treatment of occasional constipation
Materials Reviewed:	• July 21, 1997 letter to Dr. M. Lumpkin • Amendment to NDA 20-698 responding to the February 24, 1997 action letter. This amendment consists of 1. Proposed Package Insert 2. Formal Sponsor's Response 3. Safety Update 4. Protocol for Post-Treatment Evaluation of 851 Laxative in Constipated Patients
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

I. BACKGROUND/INTRODUCTION

A. Proposed Indication

Reproduced below is the wording proposed by the sponsor under the INDICATIONS AND USAGE section and the DOSAGE AND ADMINISTRATION section of the proposed Package Insert. [Other aspects of the proposed Package Insert are addressed separately].

MIRALAX®

Polyethylene Glycol 3350, NF
Powder

INDICATIONS AND USAGE

For the treatment of occasional constipation. This product should be used for 2 weeks or less or as directed by a physician.

In patients with a history of constipation, MiraLax therapy increases the volume and frequency of bowel movements.

DOSAGE AND ADMINISTRATION

The usual dose is 17 grams (about 1 heaping tablespoon) of powder per day (or as directed by physician) in 8 ounces of water, juice or other liquid. Each bottle of MiraLax is supplied with a measuring cap marked ~~to contain 17 grams of~~ laxative powder when filled to the indicated line.

Two to four days (48 to 96 hours) may be required to produce a bowel movement.

COMMENT

Constipation in general and **occasional constipation** in particular, are terms difficult to define. They both represent a change in bowel habit. **Constipation** is a symptom and not a disease. With regards to definition, **constipation** has different meanings for different people. Patients who complain of **constipation** may describe: infrequent defecation, pain or straining with defecation, passage of firm or small volume material[1], increased difficulty initiating evacuation or a feeling of incomplete evacuation. These complaints are difficult to quantify in clinical practice. Bowel frequency has been used as an objective criterion. An attempt by investigators to objectify a definition proposes <300 g stool weight weekly. However, patients reporting **constipation** may have high frequency, volume, weight or urgency. The proposed Federal Register[2] definition is <3 stools in a 7-day period. This definition is based on epidemiological studies showing that 98% of adults in the U.S. or the U.K. have stool frequencies of three or more per week. Yet, in one survey, up to 60% of subjects reporting constipation had daily bowel movements. These individuals most frequently complained of defecatory straining or a sense of

---

[1] A complaint of decreased stool bulk may have little clinical relevance, since the range for stool weight in the USA is wide, from 35 to 224 g and has marked inter- and intraindividual variaability. In rural Africa, where the average daily fiber intake is >3 times that of the USA (75 g vs 15 g), stool weight averages 470 g.

In the proposed monograph for OTC laxative, Antidiarrheal and Antiemetic Products, it is stated that the quantitation of the following variables is appropriate for the efficacy evaluation of laxatives:

- Stool FREQUENCY
  CONSISTENCY
  VOLUME
  WEIGHT
  WATER CONTENT
  SOLIDS
  DENSITY
  TRANSIT TIME
  EXCRETION RATE
  ELECTROLYTES and
  BILE ACIDS

[2] TFM for Laxative Drug Products for OTC Human Use [FR50(10):2124-2158 (1985)]. [FR 40(56):12902-12944 (1975)]

incomplete defecation. There is also the so-called **Rome Criteria** for "functional constipation". With these criteria constipation is defined by two or more of the following symptoms [present for at least 3 months]: 2 or fewer BMs per week, stool weight <35 g/day, straining in more than 25% of occasions, hard, lumpy stools on more than 25% of occasions, and sensation of incomplete evacuation on more than 25% of occasions. The CIOMS[3] definition of constipation as an ADR is either the passage of stools hard in consistency and difficult to expel, or reduced frequency of defecation in comparison to the patient's usual habit.

Schulte-Bickholt and Koch [Current Therapy in Gastroenterology and Liver Disease (1997)] consider a diagnosis of **acute constipation** in those individuals who have recently (<6 mo. previously) had either decreased frequency of BMs or increased difficulty initiating evacuation. These authors define chronic constipation as a disorder lasting 6 mo. or longer in which individuals have 2 or fewer BMs per week. Although a definition of **occasional constipation** is not provided, it is worth noting that this is an FDA recognized indication since the following products (all available OTC) include **occasional constipation** in the pertinent section of the labeling[4]: DULCOLAX® (brand of bisacodyl[5] USP; also approved for "irregularity"); PERDIEM® Fiber Therapy (bulk fiber laxative); Overnight Relief PERDIEM® (bulk fiber laxative plus natural vegetable stimulant); SENOKOT® (standardized senna[6] concentrate and docusate[7] sodium, etc.

One additional comment is that, for some laxatives, the onset of action could be up to 72h. These include the surfactant docusate and bulk-producing agents such as methylcellulose, psyllium and polycarbophil. The site of action for both types of compounds is both the small and large intestine.

> NOTE As it will be discussed later, the sponsor has carried out studies to evaluate the effect of PEG 3350 on **BM frequency** (Study 851-6) and **stool output** (weight) **plus BM frequency** (Study 851-3).

B. Drug Being Tested

The drug which is the object of the present studies is 851 laxative polyethylene glycol 3550 (PEG 3350; oral powder to be dissolved in 8 ounces of fluid). PEG 3350 is a poorly absorbed

---

[3] Council for International Organizations of Medical Sciences

[4] Section headings include: ACTION AND USES; ACTION AND INDICATIONS; INDICATIONS; INDICATIONS AND USAGE; ACTIONS -

[5] Bisacodyl is a compound with direct action on the intestinal mucosa; it stimulates myenteric plexus and alters water and electrolyte secretion.

[6] Senna is an irritant/stimulant with direct action on intestinal (colonic) mucosa.

[7] Docusate is a surfactant with detergent activity that facilitates admixture of fat and water to soften stool.

osmotic agent used in GoLYTELY and NuLYTELY (bowel cleansing agents)[8] to evacuate the colon in preparation for colonoscopy.

II. BRIEF REGULATORY HISTORY LEADING TO PRESENT SUBMISSION

On February 26, 1996 the firm submitted NDA 20-698 to market MiraLax® (PEG 3350) powder for oral solution, at a dose of 17 g, for the treatment of occasional constipation. The firm submitted the following four studies, two of which are pivotal, in support of approval:

1) **851-6**, considered pivotal by the firm, was a double-blind, parallel trial which enrolled 151 subjects who were randomized to Placebo (PL) or PEG 3350 17 g. The treatment period lasted 14 days. The primary endpoint of efficacy was BM frequency (success defined as >3 BM per 7d period, Failure defined as <3 BM per 7d period, use of laxative/enema or withdrawal); 133 subjects completed this study; 2) **351-3** the other trial considered pivotal by the firm, was a single center, double-blind, triple-crossover study which randomized 50 constipated patients to a first period (10 days) of either 17 or 34 g of PEG 3350 therapy. Subsequently, without a washout interval, subjects were randomized to second or third periods of PL or the alternate PEG 3350 dose. The primary endpoint of efficacy were stool frequency and stool weight; all patients completed this trial. 3) **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 g of PEG 3350 experienced diarrhea. Subsequently, the PEG 3350 doses were reduced to 6 and 12 g for the remaining 30 patients and 4) 851-5 was a single-center crossover study in which 25 patients were randomized to PEG 3350 17 g or PL.

Medical Officer and Statistical Reviews were completed on December 26, 1996 and September 17, 1997, respectively. In a February 24, 1997 Not Approvable letter the firm was informed that while Study 851-6 provided support for the 17 g dose of PEG 3350, the other pivotal trial (851-3) was insufficient to support approval. Further, in light of the diarrhea experienced by four of the first five elderly subjects that received 17 or 34 g of PEG 3350 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. The regulatory history includes a meeting at office level (May 8, 1997) and at least two at Center level (July 9, 1997 and March 25, 1998). Excerpts of the Summaries of the Minutes of these important meetings are reproduced below.

APPEARS THIS WAY ON ORIGINAL

[8] GoLYTELY and NuLYTELY are currently marketed in the U.S. and contain 236 g or 420 g PEG 3350, respectively, with various electrolytes. As an osmotic agent, PEG 3350 can increase the water content of the stool and produce a voluminous liquid stool when given orally. Therefore, it is expected to be therapeutically useful in constipation patients.

At the May 8, 1997 meeting, Braintree was told that as an alternative to carrying out an additional clinical trials to support Study 851-6, they could reanalyze **Study 851-3** and submit that reanalysis as their response to the clinical deficiencies in the Not Approvable letter. The July 9, 1997 meeting was requested by the firm in a further attempt to resolve the differences of opinion that existed with regard to the safety and efficacy of this product. It was the firm's position that they have made a scientifically valid case for the efficacy of PEG 17 g. 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 3350 17 g and submit these items to the NDA. Also, at this meeting, the firm was informed of the possibility of seeking guidance from the Agency's G.I. 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).

In a July 21, 1997 letter to Dr. Lumpkin, Braintree attached results of further analyses requested for **Study 851-3**. (See section II of the current MOR). Meanwhile, after a series of internal discussions, which included reviewer's opinions on the additional analyses for **Study 851-3**, it was decided a) that this trial demonstrated a dose response and b) when the totality of the available evidence was evaluated, the PEG 3350 17 g dose could be considered effective. There were, however, a number of questions that remained unanswered. These included questions on the population studied in the trials, the population in whom MiraLax® would be indicated, how it would be labeled and used, the conditions it would be used to treat and the recommended duration of treatment. At a March 25, 1998 meeting (also at Center level) and in response to the Agency's questions, Braintree discussed information, other than what was submitted in the NDA, which would answer the remaining questions about the clinical database. Included were the precise indication, characteristics of study population in the clinical trials, explanations that MiraLax is a safe drug and proposed labeling. At the end of this meeting, the firm agreed to submit complete information in response to the Not Approvable Action of February 24, 1997, which is still in effect. In addition to answers to the questions mentioned above, the firm was requested to submit a detailed proposal for post Approval studies to address 1) whether and when constipation returns after MiraLax treatment, 2) other indications, a safety update, in accordance with 21 CFR 314.50(d)(5)(vi)(b), long-term safety data from the ongoing open-label study and justification based on past discussions with the Agency, of pivotal **Study 851-3** as supportive of efficacy. The sponsor's submission, dated June 2, 1998, is the subject of the present MOR.

III. REVIEW OF SPONSOR'S SUBMISSION DATED JUNE 2, 1998

A. Contents of Sponsor's Submission

B. Further Analyses of Braintree Protocol 851-3

- This was a triple cross-over study of 50 patients. Following a 7-day placebo (PL) control period, constipated patients were randomized into three 10-day treatment periods during which all stools were collected. The definition of constipation used in the study required both a frequency and volume measurement (see below). The treatments studied were 17g 851, 34g 851 and PL. PL was not administered in the first treatment period. As mentioned above, the **primary measures of efficacy** were bowel movement frequency and stool weight.

- No interim analysis was planned or performed. A preliminary analysis based on 35 of the 50 completed patients was presented in a document titled ""NDA Outline""(submitted March 2, 1990).

- In this protocol, constipation was defined[9] as *"less than or equal to 3 bowel movements per week and/or less than 300 grams of stool per week"*.

- The **851-3** protocol did not include washout periods between the 10-day treatment periods. Instead, in anticipation of treatment carry-over, the approved protocol specified analysis of the last 7 days of each treatment period.

---

[9] According to the firm, this protocol and definition (submitted 11/23/87) were discussed and agreed upon in a meeting between Braintree and FDA on 11/5/87. The definition of constipation used was derived from that used in the Phase 1 study (Braintree Protocol 851-2a; NDA 20-698, Volume 1.4.1, page 59) and discussed in a previous meeting between Braintree and FDA on 5/29/86. In the phase 1 study a slightly less restrictive definition had been used: *"less than or equal to 3 bowel movements per week and/or less than 50 grams of stool per day"*.

- At an 8/20/90 meeting between the FDA and Braintree, the Agency recommended reanalysis using the entire 10-day treatment period and analysis for evidence of dose response between the 17 and 34 gram doses.

- Following completion of the study, in a subsequent meeting (03/09/94), FDA recommended use of a new definition of constipation as suggested in a Federal Register proposed rule (40:12902, 1975) of less than 3 bowel movements per week. Although not specified in the protocol, an attempt was made to apply this definition in the original 851-3 NDA study report (Table 3.12, in NDA 20-698, Volume 1.4.2, p.3-32). However, as correctly pointed out in the FDA Statistical Review[10], this table was constructed in error. Further analyses utilizing the Federal Register criteria are presented below.

1) First Treatment Period Comparisons (Tables 1 and 2)

- These tables depict the mean daily BM frequency and daily stool output for the placebo control period (7 days) and the first treatment period (10 days). All patients that entered the first treatment period who provided data are included[11].

TABLE 1

Mean Daily BM Frequency
Control vs First Treatment Period

	17 g			34 g	
	Control	1st Treat		Control	1st Treat
Mean	0.31	0.52		0.32	0.83
SEM	0.027	0.046		0.025	0.118
n	24	24		26	26
17 gram: Control vs 17g: t=5.40, p<0.0001 34 gram: Control vs 34g: t=4.16, p=0.0003 17g vs 34g: t=248, p=0.019					

APPEARS THIS WAY ON ORIGINAL

[10] The FDA Statistical and Clinical Reviews stated that the analyses submitted for 851-3 in the NDA were based upon the last 7 days of each treatment period. As discussed above and indicated in the 851-3 study report, the analyses submitted in the NDA included all 10 days of each treatment period. No last 7 day data analysis was submitted.

[11] The sponsor stated that Tables 1 and 2 were constructed from data submitted in the NDA (Study 851-3 case report tabulations in NDA 20-698, Volume 1.4.2).

TABLE 2

Mean Daily Stool Output
Control vs First Treatment Period

	17 g			34 g	
	Control	1st Treat		Control	1st Treat
Mean	27.9	45.1		29.8	93.5
SEM	4.14	6.64		4.39	14.65
n	24	24		25	25
17 g: Control vs 17g: t=2.71, p=0.013 34 g: Control vs 34g: t=4.67, p=0.0001 17g vs 34g: t=3.00, p=0.005					

As explained by the sponsor, the paired data analysis shown in Tables 1 and 2 includes control period results. Here, the mean response of the 24 patients that received 17 g 851 in the first 10-day treatment period is compared with their response to PL in the 7-day control period. Similarly, the mean response of the 26 patients that received 34 g 851 in the first treatment period is shown with their response to PL in the control period.

COMMENT

The reviewer agrees with the sponsor. Tables 1 and 2 show substantial and highly statistically significant differences (paired t-test) between the response to the first treatment period laxative therapies and the response to the control period PL. In addition, a statistically significant dose dependent response is demonstrated between the 17 g and 34 g 851 doses in the first treatment period by unpaired t-test. This provides evidence of laxative efficacy according to the criterion of the 8/20/90 meeting.

These data, comparing the control to the first treatment period, provide evidence of laxative efficacy for the 17 g 851 dose. Whether the parameter of evaluation is mean daily BM frequency or mean daily stool output, the 34 g 851 dose is superior not only to control but also to the 17 g 851 dose.

2) Success/Failure Analysis (Table 3)

- In these analyses, constipation was defined as *"less than or equal to 3 BMs per week and/or less than or equal to 300 g of stool per week"*. Therefore, successful treatment was defined as "*greater than 3 BM per week and greater than 300 g of stool per week". For a 10-day treatment period the success threshold would be 4 BMs and 429 g of stool.*

TABLE 3

First Treatment Period Responses vs Placebo Control
Braintree 851-3 Study Criteria

	17 gram			34 gram	
	Control	1st Treat		Control	1st Treat
Success	0.0% (0)	E37.5% (9)		0.0% (0)	69.2% (18)
Fail	100% (24)	62.5% (15)		100% (26)	30.8% (8)

17 gram: Control vs 17g: χ^2=11.1, p=0.0009 (Fisher Exact p=0.0008)
34 gram: Control vs 34g: χ^2=27.5, p<0.0001 (Fisher Exact p<0.0001)
17 g vs 34 g: χ^2=5.06, p=0.025 (Fisher Exact p=0.046)

Success/Fail Criteria

Fail:

Control (7 days): ≤3 BMs and/or ≤300 g stool
Treatment (10 days): ≤4 BMs and/or ≤429g stool

Success

Control (7 days): >3BMs and >300g stool
Treatment (10 days): >4BMs and >429g stool

In this Table, the first 10-day treatment period responses to 851 laxative are compared to the PL control period. All patients received PL during the 7-day control period. The patients were then randomized to a treatment period where they received either a 17 g daily dose of 851 laxative or a 34 g daily dose for 10 days. Control and treatment data for patients that received 17 g 851 in the first treatment period are shown separately from patients that received 34 g 851.

COMMENT

In this analysis, treatment success and failure were defined according to a stringent study criteria where both stool frequency and volume are taken into account. The reviewer agrees with the sponsor's conclusions. As in the frequency and stool output tables (1 and 2), the data in Table 3 show substantial and highly statistically significant differences in patient success between the first treatment period and the control period. In addition, a statistically significant dose-dependent difference in response between the 17 and 34 g doses is again demonstrated in the first treatment period.

APPEARS THIS WAY ON ORIGINAL

3. Other Comparisons (Tables 4 to 6)

- Tables 4 and 5 show results of BM frequency analysis[12] using a t-test for repeated measures for correction for multiple comparisons.[13] These tables depict the results of a repeated measures analysis of the 10-day treatment periods for those patients that completed at least four days of treatment for the respective treatment periods in each analysis. The differences between all of the treatments are highly statistically significant for both BM frequency and stool weight. A highly statistically significant dose response for both BM frequency and stool weight is also demonstrated.

- The sponsor notes that, as prospectively specified in the protocol, study participants were evaluated in a 7-day PL control period in which only those that had *"less than or equal to 3 BMs per week and/or less than or equal to 300 g of stool per week"* were enrolled. With such a definition of constipation, one would clearly expect that many of the enrolled patients would *a priori* fail a 2 BM or less success/fail criteria.[14] An appropriate analysis applies the protocol constipation criteria as in Table 3 (above) to each of the 10-day treatment periods. An intent-to-treat analysis using the study criteria for the 17 g dose is presented in Table 6. According to this criteria, only about 20% of PL recipients had a "successful" result whereas 52% of the 17g 851 recipients were successfully treated. This result is highly statistically significant.

APPEARS THIS WAY ON ORIGINAL

[12] This analysis, as presented in FDA Statistical Review Tables 11 and 12 (pages 20 and 22 of the FDA Statistical Review) were based upon applications of tests for independent means including a t-test. According to the sponsor, such tests lack statistical power to determine real differences **where repeated measures are taken**. In the 851-3 study each enrolled patient was treated with three different medications (PL, 17 g 851, 34 g 851) during three consecutive 10-day treatment periods.

[13] [G.A. Millikin: Analysis of Messy Data. Wadsworth, Inc. (1984)]

[14] As applied in the FDA Statistical Review, Table 11.

TABLE 4

Mean Daily BM Frequency
Repeated Measures t-Test
(4 or more days of 10 day data)

Comparison	PL	17 g	34 g	n	t	p
PL vs 17g	0.45	0.58		47	3.80	0.0004
SEM	(0.03)	(0.04)				
PL vs 34g	0.44		0.80	42	4.00	0.0003
SEM	(0.04)		(0.09)			
17g vs 34g		0.54	0.81	42	2.93	0.006
SEM		(0.04)	(0.09)			

Bonferonni adjustment for multiple comparisons:

Observed Result	Adjusted Value
p = 0.0003	p = 0.0013
p = 0.0004	p = 0.001
p = 0.006	p = 0.02

TABLE 5

Mean Daily Stool Weight (grams)
Repeated Measures t-Test
(4 or more days of 10 day data)

Comparison	PL	17 g	34 g	n	t	p
PL vs 17g	36.5	59.1		46	4.46	0.0001
SEM	(4.96)	(6.23)				
PL vs 34g	39.0		81.4	41	6.80	<0.0001
SEM	(5.56)		(9.01)			
17g vs 34g		56.5	82.3	40	4.36	0.0001
SEM		(6.75)	9.15)			

Bonferonni adjustment for multiple comparisons:

Observed Result	Adjusted Value
p = 0.0001	p = 0.0003
p < 0.0001	p < 0.0003

APPEARS THIS WAY ON ORIGINAL

TABLE 6

Treatment Success analysis
(Intent-to-Treat 10 days)

Criteria	PL	17 g
Success	10 (20.4%)	26 (52%)
Fail	39 (79.6%)	24 (48%)
Fail: (10 days): ≤4 BMs and/or ≤429g stool *Success:* (10 days): >4 BMs and >429g stool		

COMMENT

Because in Study 851-3, patients enrolled were treated with three different test medications and repeated measures were taken, the reviewer agrees that a t-test for repeated measures with corrections for multiple comparison is appropriate. Furthermore, the highly significant results in Tables 4 and 5 are obtained in spite of an enhancement of the PL response. This enhancement is due to the cross-over effects which – as noted in the FDA statistical Review – would tend to obscure laxative efficacy.

In addition, it is worth mentioning that based on the experimental approach specified in the protocol, analysis of 10-day data (Tables 4 to 6) is more appropriate than analysis of the first 7-day treatment period. This is because the 851 laxative is not expected to act rapidly [as would a saline cathartic or irritant][15]. Instead, as expected, the drug action can take several days to develop[16]. As shown below, in **Study 851-3,** a majority (73%) of patients had at least one BM by the second day of therapy.

APPEARS THIS WAY ON ORIGINAL

[15] These compounds/formulations have a different mechanism of action. For magnesium-containing compounds the onset of action (OOA) varies between 0.5 to 3h, for sodium phosphate/biphospate, 0.03 to 0.25h. Irritant/Stimulants such as cascara, senna, phenolphthalein, bisacodyl tablets, the OOA is 6 to 10h; bisacodyl suppository (0.25 to 1h) and for castor oil the OOA is 2 to 6h.

[16] Examples of laxatives where the drug's OOA may take several days include: docusate (24 to 72h), lactulose (24 to 48h) and the bulk producing laxatives (up to 72h) including methylcellulose, psyllium and polycarbophil.

Days to First BM
Braintree Pivotal Studies
17 gram 851 Dose

Study	Measure	Day 1	Day 2	Day 3	Day 4
851-3	Pt W/BM	23	35	42	45
(n=48	%	47.9%	72.9%	87.5%	93.8%
851-6	Pt w/BM	28	48	59	63
(n=76)	%	36.8%	63.2%	78.9%	84.2%

This table shows the cumulative number of patients ("Pt w/BM") who had at least 1 BM up to the fourth day of therapy with 17 g 851 daily. For both studies, the majority of patients had at least one bowel movement by the second day of therapy.

These findings appear to justify the protocol specified a 10-day treatment period. In the report for the 851-3 study submitted in the NDA all of the analyses were for the entire 10-day treatment period. Thus, results of the success/failure analysis according to the study enrollment criteria (10-day period) document a clinically significant therapeutic gain (32%) of the 17 g 3350 dose over PL.

C. Braintree Protocol 851-5

This reviewer has nothing to add to the FDA analysis carried out by the MO and statistician reviewers.

D. Braintree Protocol 851-6

Ibid.

E, Other Safety Considerations

1) Older Patients

There were no reports of diarrhea or loose stools associated with the 6 and 12 g 3350 doses.

- Of a total of 161 constipated patients that received 17 g 851 laxative for 10 to 14 d (Protocols 851-3, -4, -5 and –6) 24 were age 65 or older. Of these, three experienced diarrhea (an additional 9 that experienced diarrhea at the 17 g dose were younger than age 65).

  - 2 of the older patients were from the 851-4 study (study subjects #4 and #5), which enrolled nursing home patients.

  - The third was from the 851-5 study (patient #18).

- The first 5 patients of the 851-4 nursing home study received 17 and 34 g 851 doses in a protocol identical to the 851-3 protocol (NDA 20-698, Volume 1.4.2).

Due to the occurrence of diarrhea in these patients the doses were reduced to 6 and 12 g for the remaining study patients. Although a dose response was not demonstrated in this study, statistically significant differences in BM frequency and stool output between the placebo control period and the first treatment period were obtained (Table 4.8 in NDA 20-698, Volume 1.4.2, page 4-27).

- On overall analysis by age of patients that experienced diarrhea (Table 7) showed no statistically significant differences in the ages of those patients that experienced diarrhea in comparison to those who did not while taking 17 g 851 per day.

TABLE 7
Protocols 851-3, -4, -5 and –6

Diarrhea vs Age
17 g Dose

	Diarrhea	None
Mean Age	43.2	44.4
SD	21.7	15.1
n	12	149
t = 0.26, p=N.S.		

Open-Label Study 851-4a Mobil Center[17]

- In this study, 136 patients were enrolled for ad-lib treatment with 851 laxative for an unlimited time period starting in 1988.
- The average recorded dose throughout the trial was 17 g or less.
- 16 of these patients had used 851 for 5 years or longer.
- No AEs with respect to therapy duration, race or age were observed except that older nursing home residents tended to use a reduced dose. As discussed in the study report, there was no tendency for the daily dose to increase over time.
- Furthermore, this study included 21 nursing home patients and 19 of these were age 65 or older.

[17] Study Report in NDA 20-698, Volume 14.4; Final Report in Volume 2.2 of June 2, 1998 Submission).

- As shown in Table 8, a 12-g dose was the most frequent starting dose. The dose used most often by nursing home residents after one and two months of therapy was also 12 g. No diarrhea was reported for these patients during the first two months of "maintenance" therapy.

TABLE 8

Nursing Home Patients Maintained at Various 851 Doses
(851-4a Mobile Center)

	DAILY DOSE (g)			
	6	12	≥17	Average
Start	2	15	2	12.6
1 month*	4	12	3	13.2
2 month*	4	9	2	12.7
* or last recorded dose				

COMMENT

The results of Study 851-4a Mobil Center are of interest because they show that 851 a) has no potential for tachyphylaxis and b) is safe and well tolerated in nursing home patients, at a daily dose of 12 g. Although not clearly established, this daily dose (12 g) seems probably effective.

2) Pediatric Patients

- The sponsor notes that no pediatric studies have been published or performed in support of the 851 NDA. Several studies have been published on use of the PEG based lavages in children for bowel preparation and a pediatric indication has been approved as safe and effective for NuLYTELY (NDA 19-797, S-006). NuLYTELY is composed primarily of PEG 3350. In general, pediatric bowel preparation with PEG-based lavage requires doses similar to adult doses (3 to 4 liters).

COMMENT

- The reviewer agrees with the sponsor's conclusion "since the mechanism of action of lavage and laxative are similar (osmotic retention of water in the gut) it is reasonable to expect that the pediatric experience with 851 laxative will be similar to the adult."

IV. SAFETY UPDATE

This section consists primarily of safety data from studies 851-4a and 851-8 which have been completed since the original submission of the MiraLax application (NDA 20-698) on February 26, 1996. In addition, recent literature data are discussed.

1. Short- and Long-term Exposure (Tables 9 and 10)

- Table 9 summarizes the 851 laxative short-term exposure experience. Included in this Table is information on a total of 348 patients exposed to 851 at various doses for 10 to 14 days. [NOTE: Data from Protocol 851-8 were not included in this Table since exposure was limited to 7 days (44 patients at 34 g/day). Nonetheless, only one pt. (#11) withdrew from this study due to an AE (nausea). This pt. withdrew following PL treatment].

- Table 10 summarizes 851 extended exposure at each dose by study center up to two years of therapy. The information in this Table is derived from the 851-4a trial, discussed below. The Mobile study center maintained well documented dosing records, therefore more detail is available for these patients. The actual doses utilized by the Detroit and Portsmouth NH study centers is approximate since this information was not consistently documented. However, all patients at the Detroit and NH centers were started on 17g 851 daily and generally instructed to maintain this dose throughout therapy.

APPEARS THIS WAY ON ORIGINAL

TABLE 9

Summary of 851 Short Term Exposures
Braintree Laboratories Protocols

Study	Measure	Dose 851 Taken (g)					All Doses
		6-9	12	17	24	34-36	
851-3 (10d study)	# Patients Started	--	--	49	--	50	--
	# Patients with 10d exposure	--	--	46	--	38	84
	Mean days exposure	--	--	9.5d	--	8.6d	--
851-4 (10d study)	# Patients Started	28	24	5	--	5	--
	# Patients with 10d exposure	22	22	3	--	2	49
	Mean days exposure	9.1d	9.5d	8d	--	5.4d	--
851-5 (14d study)	# Patients started	--	--	25	--	--	--
	# Patients with 10-14d exposure	--	--	24	--	--	24
	Mean days exposure	--	--	13.8d	--	--	--
851-6 (14d study)	# Patients started	--	--	76	--	--	--
	# Patients with 10-14d exposure	--	--	69	--	--	69
	Mean days exposure	--	--	13.3d	--	--	--
851-4a	# Patients started	2	17	104	--	--	--
	# Patients with 10-14d exposure	8	11	96	3	4	144
Total 10-14d exposure	# Patients	30	33	238	3	44	348

APPEARS THIS WAY ON ORIGINAL

TABLE 10

Summary of 851 Extended Use Exposures
Braintree Protocol 851-4a

Study Center	Daily Dose	Start	Number of Patients at Dose					
			2 wk	1 mo	2 mo	6 mo	1 y	2 y
Mobile	Mean Dose	15g	16.6g	16g	15.2g	14.3g	14.8g	16.5g
	<9g	2	8	8	9	8	6	4
	12g	17	11	10	8	7	3	3
	17g	34	31	25	22	12	9	7
	24g	-	3	1	2	1	2	4
	>33g	-	4	4	2	1	0	0
Detroit	~17g[a]	50	46	44	41	32	31	25
NH	~17g[b]	20	19	18	18	15	13	8
Total	~17g[c]	104	96	87	91	59	53	40

a,b,c) Approximate daily dose for Detroit and Portsmouth NH centers

2. Braintree Protocol 851-4a

- This trial allowed for ad-lib, unlimited duration use of 851 laxative. The study population consisted of constipated patients that had either completed the controlled clinical trials[18] (Braintree Protocols 851-3, -4, -5, and –6) or were identified for enrollment by study investigators on the basis of clinical worktop for constipation.

- 136 patients have been enrolled in the extended use protocol since it began in January 1988, spending an average of 28 months on therapy.

  - 16 patients have used 851 on an ad-lib basis for 5 years or more.
  - 33 patients remain on therapy at this time.
  - As of January 1998 the study includes over 300 patient years of therapy (Volume 2.2; this submission).

APPEARS THIS WAY ON ORIGINAL

[18] According to the protocol, study participants were given a supply of 851 laxative which they could use according to their perceived needs. Patients were monitored monthly for the first year and then quarterly thereafter. Blood samples were taken for analysis at each clinic visit. Study subjects maintained bowel movement diaries where they recorded daily bowel movements and associated symptoms (ease of passage, cramping, etc.). In addition they recorded other symptoms and problems in their diaries.

Unexpected AEs on Therapy (Table 11)

- As summarized in this Table, there have been 13 AOTES (unexpected adverse on therapy events) since August 1985. As noted, none of the unexpected AOTES was considered by study investigators to be related to test medication.

TABLE 11

Unexpected AOTES
Braintree Protocol 851-4a

Patient ID	Gender, Age	Therapy Start-End	AOTE Date	AOTE	Related to Drug
32[a]	F, 102	3/27/90-2/9/97	2/9/97	Death: cardio-respiratory arrest	NO
107	F, 70	4/93-continue	11/18/95	Black stool Pt. note. Guaiac negative	NO
111	F, 71	5/93-continue	2/96	Autoimmune hepatitis vasculitis: treated	NO
113	F, 54	7/93-10/97	10/20/97	Coronary artery bypass	NO
116	F, 57	10/93-continue	2/27/96	URI: tx with amoxicillin	NO
121	F, 46	1/94-4/98	8/26/95	Hysterectomy	NO
			4/16/97	UTI: Treated	NO
130	M, 70	6/94-continue	9/13/95	Chest pain Unstable angina	NO
			9/95	Diverticulosis Diagnosed BE & flex sig	NO
135	F, 48	11/94-continue	2/6/97	Lupus flare patient note. Pre-existing	NO
146	F, 68	9/95-3/96	3/3/96	Ischemic colitis Thrombocytosis; HTN	NO
147	F, 52	12/95-continue	3/13/96	Anemia colonoscopy negative	NO
			9/96&97	Hemorrhoid bleeding ligated.	NO

a) Pt. had a Hx of heart disease and received 851 treatment for 7 years. Cause of death was congestive heart failure following hospitalization for Xanax toxicity.

Patients 1-65 • Center 1; 101-151 • Center 2, which reported the majority of AEs.

FDA Forms 3500A for these patients were included in sponsor's Appendix B of the June 2, 1998 submission.

Expected AEs on Therapy (Table 12)

- As shown in this Table, 19 patients reported a total of 22 expected AOTES over a 3-y period, mostly as notations made by the patients in their BM diaries.

- 5 of these 22 expected AOTES were attributed to various causes other than test medication. A tally of these AEs is given below.

  - 9 involved notations of constipation or diarrhea and loose stools
  - 6 were complaints of abdominal pain, cramping or nausea
  - 5 consisted of sensations of bloating and gas
  - 1 was due to hemorrhoid inflammation.

- Some of the above-listed complaints were recurring but all resolved either spontaneously or with dose adjustment.

TABLE 12

Expected AOTES
Braintree Protocol 851-4a

Patient No.	Gender, Age	Therapy Start-End	AOTE Date	AOTE Comment	From Pt. Notes
106	F, 54	4/93-continue	4/30/96	Constipation, sinus infection: due to bacteria	YES
107	F, 68	4/93-continue	Various	Constipation, cramps, diarrhea	YES
108	F, 65	4/93-continue	12/95	Abdominal pain, constipation: due to barium from exam.	YES
			11/12/96	Diarrhea mild	YES
112	F, 58	6/93-continue	Various	Constipation, cramping: Took nonstudy laxatives	YES
113	F, 52	7/93-10/97	9&10/95	Cramping, gas:	YES
116	F, 55	10/93-continue	Various	Nausea, abdominal discomfort	YES
117	F, 57	11/93-continue	12/96	Stomach pain: Irritable bowel	YES
118	F, 58	1/94-continue	Various	Pain: abdominal	YES
121	F, 43	1/94-continue	Various	Abdominal pain Reflux, diverticulitis	YES
124	F, 45	1/94-9/97	8/17/97	Cramping, loose stools, reduced dose	YES
			4&5/97	Bloating, stomach ache	YES
125	M, 75	12/93-11/98	8-10/95	Bloating, gas: mild	YES
130	M, 70	6/94-continue	10/12/95	Constipation:	YES
137	F, 49	9/94-continue	3/16/96	Diarrhea: due to Bioxin	YES
			8/27/97	Gas, abdominal distension:	YES
138	F, 35	9/94-continue	10/16/95	Inflammation of hemorrhoid	YES
142	F, 39	10/94-continue	Various	Bloating, diarrhea: dose changed	YES
147	F, 51	12/95-continue	Various	Constipated, diarrhea, fullness, discomfort: dose varied	YES
148	F, 78	12/96-12/96	2/27-96	Diarrhea: side effect of other med.	YES
150	F, 29	4/96-7/97	Various	Bloating: cramping	YES
151	F, 36	9/96-continue	10&11/96	Loose stool varied dose	YES

Patients 1-65 • Center 1: 101-151 • Center 2

- As described in the study report, no differences with respect to age or race were evident except that elderly nursing home residents tended to use a lower dose (12 g). Also, no relationship was apparent between therapy duration and reported AEs. As already mentioned, no tachyphylaxis was observed.

- 34 high risk patients (defined as having medical histories of heart disease, renal failure, diabetes and hypertension) were enrolled in the study (including 15 nursing home patients).

  - These patients tended to be older than the study group as a whole (68 y vs 53 y). However, their average time on therapy (30 months) was not significantly different from the study group (28 months).

3. Braintree Protocol 851-8[19]

- This protocol enrolled 57 patients treated with methadone who stated a requirement for laxative . Following a 7-day control period study subjects were randomized to a double blind, three period (7 days each) treatment schedule where they received one of three possible daily treatments (34 g 851, 30 ml lactulose or PL). Patients maintained a diary recording BMs and subjective symptoms.

- There were no AOTES reported in association with 851 laxative therapy.

- 3 AOTES (one unexpected) were reported during PL or lactulose treatment.

4. Recent Literature Publications

- 5 clinical trials[20] utilizing PEG and electrolyte formulations (PEG-ELS) or PEG alone for treating constipation have been published [four in abstract form; reprints were included in sponsor's Appendix A]. In these studies, 168 constipated patients received PEG at various daily doses for two to eight weeks. Some of these studies were European trials where polyethylene glycol is identified as PEG 4000. The sponsor notes that European PEG 4000 is identical to PEG 3350. The difference is only in nomenclature; both are usually referred to as "PEG". A further complication is that some studies refer to PEG and PEG-ELS synonymously.

- Few AEs were observed and no differences from PL or alternate therapies with respect to AEs were noted.

COMMENT

The information included by the sponsor in Safety Update in submission of June 2, 1998, does not reveal findings of concern. A total of 348 patients have received graded doses of 851 short-term (10 to 14 days). By now, a total of 40 patients has received up to 16.5g of 851 daily for 2

---

[19] Only safety data are briefly reviewed here. The complete study report was included in Volume 2.2 of the June 2, 1998 submission.

[20] [A. Attar et al. : Comparison of low-dose polyethylene glycol (PEG) and lactulose in chronic constipation. Gastroenterology 110:A625 (1996)]
[E. Corazziari et al.: Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. Dig. Dis. Sci. 41:1636-1642 (1996)]
[H. Hudziak et al.: Low dose of polyethylene glycol 4000: Digestive effects in healthy subjects. Gastroenterology 110:A683 (1996)]
[M. Lehmann et al.: Low-dose polyethylene glycol (PEG) in chronic constipation: double blind placebo-controlled crossover trial. Gastroenterology 110:A704 (1996)]
[R. Lopes et al.: Two doses of oral PEG 4000 vs enteroclysm in the treatment of severe refractory constipation in mentally handicapped patients. A cost-effectiveness analysis. Gastroenterology 112A27 (1997)]

years. These long-term data originated from two main sources: Protocol 851-4a, and five recent literature publications. None of the unexpected adverse on therapy events (some serious, including one death due to cardiorespiratory arrest) were thought to be due to PEG 3350 administration. Expected adverse on therapy events consisted primarily of gastrointestinal symptomatic manifestations related to constipation, the symptom being treated. Included among these AEs were abdominal pain, cramping, gas, nausea, abdominal discomfort, bloating and fullness. Also included were instances of what appeared to be too much a pharmacodynamic effect (i.e. diarrhea) or inadequate therapeutic effect (i.e. constipation). But, according to the information provided by the sponsor, patients continue 851 laxative medication in spite of these AEs. Few instances of withdrawal due to drug per se were documented but the incidence of these is not of concern.

The possibility of serious ADRs with doses of 851 higher than the recommended 17 g daily, especially in fragile elderly patients is still of some concern but this concern can be appropriately addressed in the labeling.

V. PROTOCOL 851-9 (PHASE 4 STUDY)

"Post-treatment Evaluation of 851 Laxative in Constipated Patients"

1. Design/Objective

- This open-label, multicenter trial is designed to address the question as to what therapeutic course is followed by constipated patients after a 14-day 851 laxative course of therapy at a dose of 17 g/day.

2. Study Population

- The study population (see characteristics in Table 13) is adequate for the proposed study.

TABLE 13
Braintree Protocol 851-9

Characteristics of the Study Population

INCLUSION CRITERIA	REASON FOR EXCLUSION
• Healthy, constipated male or female outpatients (n=100) who are 18y of age or older and who have signed an IC and given a medical health history. • History of non-organic constipation of at least 12 months. [minimum evaluation will include a P.E. and a stool for occult blood; additional evaluations are left to the discretion of the investigators but should be consistent with good medical practice]. • Patients will be pre-qualified for inclusion into the trial if they meet 2 or more of the following "Rome" criteria present for at least the previous 12 months[a] [1] Straining on at least 25% of BMs [2] Feeling of incomplete evacuation after at least 25% of BMs. [3] Hard of pellet stools on at least 25% of BMs. [4] On average, stool less frequent than 3 per week.	• History of gastrointestinal obstruction or other organic cause of constipation. • Women of child-bearing potential who do not have a negative pregnancy test/ • Lactating females. • History of gastric retention, bowel perforation, toxic colitis, megacolon. • Bowel resection or colostomy. • Those who in the opinion of the investigator should not be included in the trial. • Inability to understand IC and/or to complete a self-assessment form.
a) [W.E. Whitehead et al.: Report of an international workshop on management of constipation. Gastroenterology International 4:99-113 (1991)]	

3. Summary of Proposed Study Execution

- Qualified subjects will receive 851 laxative for a 14 day period. Each day the subject will take 17 g of test medication (using a marked measured cap from the medication bottle).
- After the treatment period the patient will return the unused medication (which will be measured to estimate compliance).
- On a daily basis, subjects will report "Rome" criteria symptoms including bowel movements, straining, incomplete evacuation and stool consistency (hard or pellet) as well as laxative use via a telephone data gathering system.
- Use of laxatives or medications which might interfere with the conduct of the study will be discouraged during the 851 treatment period.
- If the subject has no BM during the treatment period and a laxative is administered (other than the test medication), he/she will be considered to have failed the treatment.

- Diarrhea, defined as more than three large watery stools per day (i.e. patient subjective evaluation of abnormally large, watery bowel movements) will be scored as a treatment success (as well as an AE).

    - If a subject experiences continuing diarrhea or fails the treatment, the treatment will be discontinued.

- Treatment efficacy will be defined as those patients who no longer meet 3 or more of the "Rome" criteria during the two week interval.

- Investigators and study subjects will score the test medication treatment period as to whether the therapy was effective and satisfactory.

4. Follow-up Period (56 days)

- On a daily basis for 8 weeks following the test medication treatment period, study subjects will report "Rome" criteria symptoms including BMs, straining, incomplete evacuation and stool consistency (hard or pellet) as well as laxative use via a telephone data system.

5. After Study Completion

- Qualified study subjects will be offered a barium enema or sigmoidoscopy following the completion of the trial (unless done within the previous 2 years or if a colonoscopy was done within the previous 2 years).

6. Proposed Reporting of ADRs and Discontinuation of Study

These are adequate.

7. Data Analysis

- As noted by the sponsor in Section H of the proposed Protocol, 851 laxative efficacy will be demonstrated by observing treatment success resulting from 851 laxative use as compared to the post-treatment period.

- The results of treatment and follow-up periods will be evaluated according to modified "Rome" criteria based on a two week interval:

    [1] Straining on at least 25% of bowel movements
    [2] Feeling of incomplete evacuation after at least 25% of BMs
    [3] Hard or pellet stools on at least 25% of BMs
    [4] On average, stool less frequent than 3 per week.

- There will be one two week treatment interval and 4 follow-up intervals (2 weeks each).
- A treatment success will be defined as a patient not meeting 3 or more of these criteria during an interval.
- "Rome" criteria data will be tabulated and descriptive statistics provided as appropriate.
- Population demographics will also be reported using descriptive statistics.

8. Drug Inventory/Disposition, Study Monitoring, Documents and Notifications

These and other aspects of the proposed study are adequate.

COMMENT

Study 851-9 is set to evaluate the post-treatment status (56 days) in constipated patients subsequent to a 14-day 851 laxative course of therapy at the recommended dose of 17 g/day. The design and proposed execution of this Phase 4 trial are adequate to meet the study objective. Laxative efficacy will be demonstrated by observing treatment success. The latter will be evaluated according to modified "Rome" criteria based on a two week interval: one two-week treatment interval followed by 4 follow-up intervals of 2 weeks each.

The sponsor needs to provide the specific statistical methods to be used in analysis of data.

VI. CONCLUSIONS

1. Further statistical analyses of data from pivotal Study 851-3 have demonstrated that, at the daily dose of 17 g, PEG 3350 is an effective treatment of occasional constipation. Results of these evaluations confirm those from Study 851-6, a trial that provided support for the 17 g dose of PEG 3350.

2. The additional information in the sponsor's June 2, 1998 submission, including data in older patients (clinical protocols 851-3, -4, -5 and –6), results of open-label study 851-4a Mobil Center and a Safety Update **support** the safety of the 17 g recommended dose. Safety information on recent literature publications lends additional support to this conclusion.

The above conclusions justify the Recommendations for Regulatory Action that follow.

VII. RECOMMENDATION FOR REGULATORY ACTION

1. Approval of MiraLax® (polyethylene glycol 3350 NF) for the treatment of occasional constipation.

   This recommendation is based on results of Study 851-6 which are supported by those of Study 851-3. Whereas Study 851-6 showed effects of 851 in BM frequency, Study 851-3 studied stool weight (stool output in grams) and BM frequency. Study 851-3 not only supported efficacy as a pivotal trial but also did it in such a manner that tested another clinically relevant definition of constipation, treated in the short-term.

2. The usual recommended dose is 17 g (about 1 heaping tablespoon) of powder per day in 8 ounces of water, juice or other liquid.

3. The length of treatment is two weeks or less.

4. Other labeling issues, including adjustment of the dose in elderly patients, and MiraLax® delayed onset of action (48 to 96h), and being addressed separately.

5. The design and proposed execution of proposed Phase 4 study 851-9 are adequate. The sponsor should provide the specific statistical methodology to be used in the analyses of data.

August 25, 1998

/S/ [redacted]

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-698
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
r/d 8/17/98 jgw
f/t 8/25/98 jgw
N/20698808.0HG

Concur /S/ [redacted] 8-26-98

APPEARS THIS WAY ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

ADDENDUM TO MEDICAL OFFICER"s REVIEW

MAY - 1 1997

NDA: 20-698

Sponsor: Braintree Laboratories, Inc.

Drug: "851" PEG 3350 Laxative, powder

Indication: Treatment of Occasional Constipation

Date Received by CDER: February 28, 1996

Date Received by DGCDP: March 1, 1996

Date Received by Medical Officer: March 3, 1996

Usere Fee Due Date: February 2, 1997

Date Medical Officer Review Completed : December 12, 1996

Date Of Non-Approvable Letter from DGCDP to Braintree: February 24, 1997

Date of Present Addendum to Medical Officer's Review: May 1, 1997

Medica Officer: Dr. Rober Prizont, MD

1. On Page 20, last paragraph, my comments read as follows: *"The statistician performed this later analysis to comply with the recommendations from the DGCDP Director stated in the meeting with Braintree on Augus2 20, 1990 (see Page 3, Appendix 3, this review)".* Appendix 3 included only Pages 1-3 of that meeting.

2. AMENDMENT. The last line of this paragraph should be changed as follows (changes are shown in bold): *in the meeting with Braintree on August 20, 1990* (see **Pages 4 and 5, Appendix 3,** this review).

The Complete Appendix 3 is included as Attachment 1 of this Addendum.

/S/ [redacted]

Robert Prizont, M.D.

cc:
NDA 20-698
HFD-180
HFD-180/LTalarico
HFD-180/RPrizont
HFD-180/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 5/1/97 jgw
MED\N\20698705.0RP

/S/ 5-1-1997

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT 1

7 Page(s) Redacted
Trade Secret/
Confidential Commercial