

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020698

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

McNeil

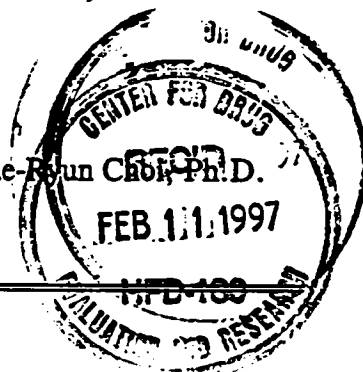
CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-698

SUBMISSION DATE: 1/16/97

Miralax (PEG 3350) Powder for Reconstitution.
Braintree Laboratories, Inc.
Braintree, MA 02185

REVIEWER: Hae-Pyung Choi, Ph.D.



TYPE OF SUBMISSION: Amendment to NDA

PRIORITY: 3 S

SYNOPSIS:

This submission is the firm's response to the information request dated 12/19/96 regarding the assay validation data for quantifying PEG 3350 in urine and stool. The following is the validation data:

PEG 3350 in Urine:

Linearity: linear from 0.04 g/L to 0.2 g/L
Precision (%CV): 2.8% at 0.2 g/L
Accuracy: 90.0% - 102.5%
LOQ: 0.04 g/L
Recovery: 103% at 0.2 g/L

PEG 3350 in Stool:

Linearity: linear from 0.2 g/L to 3.0 g/L
Precision (%CV): 3.7% at 2.0 g/L
Accuracy: 100% - 103%
LOQ: 0.2 g/L
Recovery: 99% at 2.0 g/L

Overall, the validation data is acceptable.

RECOMMENDATIONS:

The assay validation data submitted on 01/16/97 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, and found it is acceptable.

/s/ [REDACTED]

02/11/97

Hae-Ryun Choi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Lydia Kaus, Ph.D., Team Leader

/s/ [REDACTED]

2/11/97

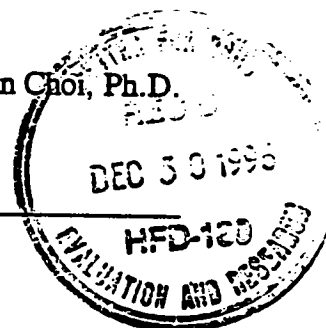
cc: Amendment to NDA 20-698, HFD-180, HFD-870 (ML.Chen, Hunt, Kaus, Choi), HFD-870 (Chron, Drug, Reviewer), HFD-340 (Viswanathan).

APPEARS THIS WAY ON ORIGINAL

McNeil

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-698**SUBMISSION DATE:** 02/26/96
05/16/96851 Laxative (Polyethylenc Glycol 3350, NF) Powder.
Braintree Laboratories, Inc
Braintree, MA 02185**REVIEWER:** Hae-Ryun Choi, Ph.D.**TYPE OF SUBMISSION:** Original NDA**PRIORITY:** 3 S**SYNOPSIS:**

The sponsor has submitted one in-vitro study, three clinical studies, and published articles in support of the human pharmacokinetics and bioavailability section of this application.

A preliminary in vitro study (protocol 851-1) showed indirectly that PEG 3350 was not fermented into hydrogen or methane by the colonic microflora in human feces; 2 g PEG 3350 was incubated with 20 ml of 1:20 fecal homogenate at 37°C for 22 hours and no hydrogen/methane was produced, while the positive control mannitol resulted in copious hydrogen production under the same conditions.

In a pilot dose-finding study (protocol 851-2a), four low doses (equivalent to 6 g, 13 g, 26 g and 52 g PEG 3350 per day, respectively) of SF-ELS (NuLYTELY) were evaluated for the laxative effects in five constipated, but otherwise normal female subjects. Following a control period, subjects were randomized to a four period treatment schedule, where they drank one of four possible daily doses of SF-ELS solution during each 7 day treatment period. Each dose was administered as a 250 ml solution. Each treatment period followed by 7 day washout period. Stool was collected, weighed (both wet and dry weight), pooled and analyzed for sodium, potassium and chloride content as well as PEG 3350. Also each bowel movement and subjective symptoms such as stool consistency, passage, cramps and flatus were recorded. The weekly stool output and frequency were analyzed by repeated measures analysis of variance. It was shown that both stool output and frequency were significantly increased as the SF-ELS dose was increased. The stool water content was also significantly increased. The results of Duncan's Multiple Range Test for stool output with respect to the dose suggested that a dose of approximately 17 g PEG 3350 would be the appropriate daily dose for laxative use. The salts in the low doses of SF-ELS tested in this study did not affect the stool electrolyte (sodium and potassium) content. The proposed formulation for laxative use would be composed of PEG 3350 only. Although stool was analyzed for PEG 3350 content, the firm failed to demonstrate the quantitative recovery after multiple dosing in constipated patients. Note that the patients were not given a lavage on the final day of treatment.

In a urine and stool recovery study (protocol 851-2b), 17 g PEG 3350 was administered daily for 2 days to evaluate the disposition of orally administered PEG 3350 in five constipated patients. Study subjects were hospitalized and stool and urine were collected for 6 days. On the final day,

the study subjects were administered a non-PEG containing lavage. The collected stool, final lavage and urine were analyzed for PEG to determine PEG recovery. PEG was not detected in the urine of any study subject using a [REDACTED] method capable of detecting 50 $\mu\text{g}/\text{ml}$. However, the recovery of PEG in stool was variable, ranged from 42.3% to 92.7% (average 72.6%); the administered PEG was only about 50% recovered in two of the five study subjects (see table below).

Subject No.	% PEG recovered
1	[REDACTED]
2	[REDACTED]
3	[REDACTED]
4	[REDACTED]
5	[REDACTED]
Mean	72.6%
SD	22.5%

It was stated that subject #5 had been unable to complete the lavage on day 6 which may contributed to the incomplete collection; no explanation was given for subject #2.

Protocol 851-2c investigated the feasibility of outpatient stool collection studies using four different non-absorbable markers. Five (2 males and 3 females) constipated but otherwise normal subjects were enrolled in the study. The markers tested were: 17 gram of PEG 3350 in 250 ml of [REDACTED] flavored water; [REDACTED] capsule (containing 24 plastic intestinal transit markers); 500 mg chromic oxide in a capsule; and 1 gram of barium sulfate in a capsule. Subjects were given four markers on the first day and stool was collected for the next 13 days. On day 13, patients were given a laxative bowel cleansing preparation. The stool and final clean-out were analyzed for the markers. The results showed the marker recovery was variable, incomplete and inconsistent in constipated patients; three subjects admitted to losing some stools. It is recognized that PEG fecal recovery may be difficult to capture in constipated patients because of the nature of the disease.

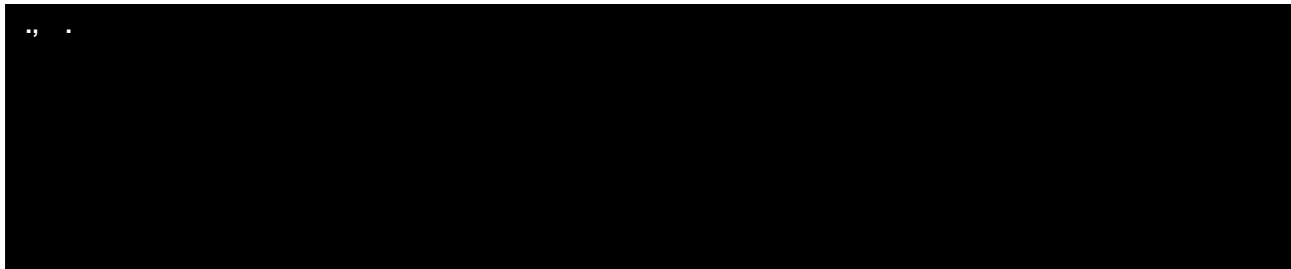
In contrast to the incomplete and variable recovery in constipated patients, a pilot study performed on four normal subjects showed that average fecal PEG recovery from the 10 g dose was about 98%.

The PEG concentrations in urine and stool were measured by a turbidimetric method which was originally developed by Hayden in 1955. The firm stated that the sensitivity of this method is 50 $\mu\text{g}/\text{ml}$ of PEG in urine, which is comparable to [REDACTED] methods. However, the [REDACTED] method has a drawback of being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. In addition, assay validation data is deficient. It lacks linearity, sensitivity, specificity, accuracy and precision information.

RECOMMENDATIONS:

The Division of Pharmaceutical Evaluation II has reviewed NDA 20-698 for 851 Laxative (submissions dated: 02/26/96 and 05/16/96) and has the following comments and recommendations:

1. The firm is recommended to develop a sensitive, selective and reproducible assay method capable of detecting PEG 3350 and its possible breakdown products in human plasma, urine and feces.



2. It is recognized that PEG fecal recovery may be difficult to capture in constipated patients because of the nature of the disease. However, the sponsors have not definitively shown that on chronic dosing PEG is not absorbed to any degree in constipated patients. Studies 851-2b and 851-2c showed that the PEG fecal recovery was incomplete and variable in constipated patients. To support the label claim of a nonabsorbable and nonmetabolizable compound, it is recommended that the firm conducts 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. The sponsors should consider using a different lavage technique to enable more complete recovery of nonabsorbed PEG. Study design protocols can be submitted to the Division for comments prior to initiation.

The medical officer(s) in HFD-180 should consider the above recommendations in light of the safety and efficacy data.

The labeling comments on page 8 should be forwarded to the sponsor.

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BACKGROUND:

NDA 20-698 for 851 Laxative (Polyethylenc Glycol 3350, NF) for the treatment of occasional constipation was submitted by Braintree Laboratories, Inc. on February 26, 1996. 851 laxative is composed entirely of polyethylene glycol 3350 (PEG 3350), having an average molecular weight of 3350. The proposed dose of 851 laxative is 17 g (about 1 heaping tablespoon) of powder per day in at least 8 ounces of fluid for a period of up to two weeks.

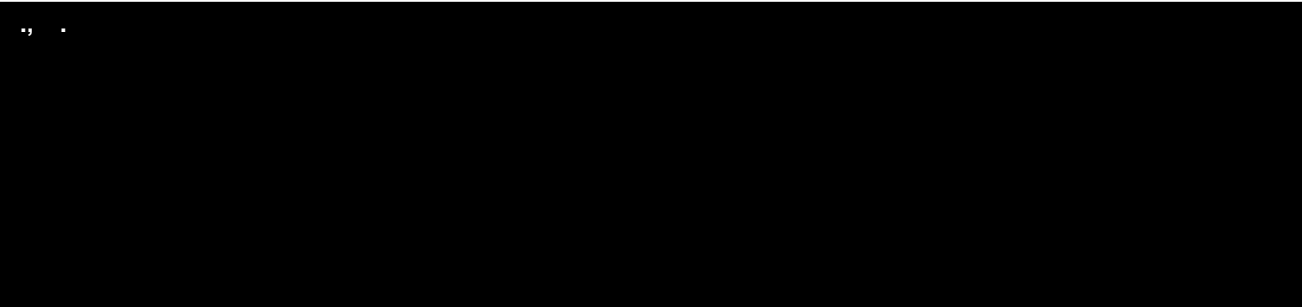
PEG 3350 is the major osmotic component of Braintree Laboratories' PEG-Electrolyte Lavage Solutions (GoLYTELY or PEG-ELS and NuLYTELY or SF-ELS) approved as NDAs 19-011 and 19-797 for bowel cleansing prior to colonoscopy and/or barium enema x-ray examination. It is reported as an inert, non-absorbable osmotic agent. Since it has no effect on active absorption or secretion of glucose or electrolytes, PEG 3350 has been used for many years as a marker in gastrointestinal research. A single dose of NuLYTELY contains 420 g of PEG 3350 and a single dose of GoLYTELY contains 236 g of PEG 3350. The proposed dose of 17 g PEG in 851 laxative represents 4% of the NuLYTELY dose of PEG 3350 and 7% of the GoLYTELY dose.

The PEG 3350 in 851 laxative is N.F. grade material, approved as an excipient for drug use and food additive. PEG 3350 is considered inert when taken by mouth.

PEGs having molecular weight ranged from 200 to 20,000 are listed in 'Inactive Ingredient Guide' as excipients for currently marketed drug products. A copy of the relevant information is provided in Appendix II.

The PEGs of average molecular weight 600 or less exist as liquids at room temperature. They are mainly used as reactive intermediates for the manufacture of fatty acid ester surfactants and as solvents for gas processing. The PEGs of average molecular weight 1000 to 2000 exist at room temperature

as soft to firm solids with low melting points. They are mainly used as bases for cosmetic creams and lotions, as well as pharmaceutical ointments and tooth paste formulations. The PEGs of average molecular weight of 3500 to 20,000 exist at room temperature as firm to hard, brittle, waxlike solids. They are used as binders, plasticizers, molding compounds, stiffening agents, and paper adhesives. The toxic effects of compounds of PEG class seem to be greatest at the lower molecular weights which are relatively well absorbed.



LITERATURE REVIEW OF PEG 3350 BIO/PK/PD CHARACTERISTICS:

I. PHARMACOKINETICS: The information in this section was obtained from the literature or sponsor. The Appendix II of this review contains the references. The published studies cited in this section have generally been conducted with PEG "4000" rather than with PEG 3350. The actual molecular weight of the "4000" material is in the range of 3000 to 3700. Accordingly, the current and correct designation of this substance based on the center of the molecular weight range, is PEG 3350. The designations are considered equivalent.

a. Absorption and Excretion: When used in large doses in gastrointestinal lavages, PEG 3350 has been shown to be absorbed in only very small amounts. In general, absorption to PEGs of differing molecular weights declines with increasing molecular weight.

DiPiro et al (1) attempted to measure the plasma levels of PEG 4000 during (and after) administration of a 4 L PEG-electrolyte lavage solution (240 g PEG) to normal subjects. The blood samples were collected up to 6 hours. Urine samples were collected up to 12 hours. PEG concentrations in plasma were analyzed using [redacted] method with a sensitivity of 10 $\mu\text{g/ml}$. No PEG was detected in the plasma. PEG was detected in most urine samples after two hours. The urine concentrations ranged from 21.3 to 1179.0 $\mu\text{g/ml}$. Approximately 0.04% of PEG was excreted in urine in 12 hours. It is concluded that PEG absorption was minimal in normal subjects who received 4 L of PEG-electrolyte lavage solution.

Brady et al (2) measured urinary excretion of PEG-3350 as a measure of absorption in ten inflammatory bowel disease patients as well as in ten normal subjects. The turbidimetric method was used for the measurement of PEG in urine with a sensitivity of 10 $\mu\text{g/ml}$. Patients were administered an average load of 168 g PEG 3350. Normal subjects were administered an average load of 522 g PEG 3350. The 24-hr urinary recovery of the orally administered load of PEG 3350 was $0.06 \pm 0.01\%$

(range 0.02 to 0.12%) in normal controls and $0.08 \pm 0.02\%$ (range 0.0 to 0.17%) in patients with inflammatory bowel disease. There was no significant increase in absorption in patients with inflammatory bowel disease.

Barker and Ferrett (3) measured the 24-hr urinary excretion of PEGs after an oral administration of 2.5 g PEG 600 and 5 g PEG 4000 in a combined single dose in 27 healthy subjects. The 95% confidence interval of the 24-hr urinary excretion of PEG 600 was 18.7-66.3% of the administered dose, indicating that PEG 600 is relatively well absorbed. The 95% confidence interval of the 24-hr urinary excretion of PEG 4000 was 0.39-2.67% of the administered dose, indicating PEG 4000 is not significantly absorbed.

Jackson et al (4) investigated intestinal permeability in eight patients with eczema and evidence of food allergy and ten with eczema alone using PEGs of molecular weights of 600 and 4000 as probe molecules. A dose of 2.5 g of PEG 600 and 5 g of PEG 4000 was administered to a fasting patient. Urine recovery of PEG was measured. Mean 24-hr urinary excretion of PEG 4000 in eczema patients was 2.88%, which was significantly higher than normal having a mean of 1.32%. There is no difference in the urinary excretion between eczema patients with or without food allergy. The urinary excretion of PEG 600 in eczema patients was not significantly different from normal.

Numerous studies have been published where small doses of PEG 3350 (usually 5 or 10 grams) have been administered both in vitro and in vivo as a nonabsorbable marker for intestinal perfusion studies. The intestinal PEG absorption was compared to various nonabsorbable dyes or markers in both human and animal systems. These studies are summarized by the sponsor and shown in the following table:

Studies of PEG absorption - Comparison with other markers

Study Method	Model	PEG Dose	PEG Recovery	Alternate Marker	Different From Marker	Ref.
Lavage (whole gut)	human (23 normal, 9 sprue, 1 whipple)	1 g/L	95% \pm 2%	phenol red	no	5
Lavage (whole gut)	human (26 normal, 9 constipated)	5 g/L	-	phenol red	no	6
Feed, then lavage	human (16 normal)	10 g	97.8% - 100%	CrCl ₃	no	7
Perfusion (jejunal)	human (23 normal)	14 C PEG	96.9% \pm 0.7%	phenol red	no	8
Perfusion	human (normal, sprue)	10 g/L	-	Indocyanine	no	9

(various)				BSP		
Perfusion (intestine)	human, dog	10 g/L	-	Indocyanine BSP	no	10
Perfusion (intestine)	rat	^{14}C PEG	96% -98.2%	phenol red	no	11
Perfusion	hamster	^{14}C PEG	94.8% - 97%	meglumine	no	12

BSP = bromsulphalein; indocyanine = indocyanine green; meglumine = meglumine diatrizoate

The references cited in the above table are listed in Appendix II. Intestinal perfusion studies showed that the recoveries of PEG when it is used as a nonabsorbable marker ranged from 95% to 100% of the perfused PEG.

Various nutritional absorption studies have added small doses of PEG 3350 (about 10 grams) to food ingested by human subjects. These studies are summarized by the sponsor and shown in the following table:

Human PEG Feeding Studies

Method	Time to Lavage	Study Subjects	PEG Dose	PEG Recovery	Ref.
Feed then Lavage	12 hrs	16 normal	10 g	97.8%-100%	7
Feed then Lavage	72 hrs	11 normal 6 diarrhea	10 g	^{14}C PEG 100%	13
Feed then Lavage	12 hrs	10 dialysis	10 g	99%	14
Feed then Lavage	6 hrs	8 normal	10 g	100% \pm 0.4%	15
Feed then Lavage	10 hrs	6 dialysis	10 g	100% \pm 0.7%	16
Feed then Lavage	10 hrs	6 normal	10 g	97% - 100%	17
Feed then Lavage	10 hrs	6 normal	10 g	98%-100%	18
Liquid meal	-	6 ileostomy	15 g	96.9% \pm 2.8%	19

The references cited in the above table are listed in Appendix II. In these feeding studies, a test meal with added PEG was eaten by the study subject. After a defined amount of time, the gut was