

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-015**

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

## Clinical Pharmacology Review

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**NDA:** 22-015 (Prescription Drug Switch to OTC)  
**Brand Name:** MiraLax  
**Generic Name:** PEG 3350 Powder  
**Dosage form and Strength:** Powder for Oral Solution and 17 grams   
**Route of administration:** Oral  
**Indication:** Occasional Constipation  
**Sponsor:** Braintree  
**Type of submission:** Original  
**Clinical Division:** Gastrointestinal Drug Division (HFD-180)  
**OCPB Division:** DCP III  
**Priority:** Standard  
**Submission date:** 12/05/05  
**OCPB Consult date:** 12/27/05  
**Reviewer:** Tien-Mien Chen, Ph.D.  
**Team leader:** Edward D. Bashaw, Pharm. D.

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### I. Executive Summary

Briantree Lab's MiraLax<sup>®</sup> (Polyethylene Glycol 3350, NF) powder for solution was approved on 02/18/99 under NDA 20-698. MiraLax contains only one component, PEG3350 powder. It is indicated for occasional constipation in adults and the dosing regimen is 17 grams (one scoopful) QD with 4-8 ounces of water, juice, soda, coffee, or tea and the solution is given orally for 14 days or less or as directed by a physician.

On 12/05/05, the sponsor submitted NDA 22-015 for switching MiraLax from prescription to OTC use. No change to the composition of MiraLax OTC was made and four sizes are packaged, 17, 119, 238, and 527 grams. Four human pharmacokinetic (PK) studies were conducted to assess single-dose and multiple PK in healthy subjects with normal renal function and in otherwise healthy subjects with end-stage-renal-disease (ESRD) plus additional PK data from a clinical study in constipated patients. The results showed that 1) after multiple oral dosing of 17 g QD x 7 days, mean recovery of PEG 3350 (up to 240 hrs) in feces was around 93% or higher and 2) < 0.6% of a PEG3350 oral dose was absorbed and excreted in urine after single or multiple doses of PEG3350 to healthy subjects.

No major differences were found in the amount of PEG3350 excreted in urine between men and women or between the young and the elderly. Similar exposure was seen between single-dose and multiple-dose PK and that between healthy subjects and constipated patients. Mean terminal half-life ( $T_{1/2}$ ) of PEG3350 was increased from 4-8 hrs (in healthy subjects or patients with normal renal function) to 38.5 hrs in subjects with ESRD (<10 mL/min) with an increased systemic exposure which is due to compromised renal excretion function and is unlikely due to a true increase in absorption.

A. Recommendations

NDA 22-015 for MiraLax (PEG 3350) oral solution has been reviewed by OCP and the NDA is found acceptable from OCP perspective. No general or labeling comments are to be conveyed to the sponsor.

B. Phase IV Commitments: None

07/17/06

Tien-Mien Chen, Ph.D.  
Division of Clinical Pharmacology III

Team Leader

Edward D. Bashaw, Pharm.D. \_\_\_\_\_ 08/07/06

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## III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Briantree Lab's MiraLax<sup>®</sup> (Polyethylene Glycol 3350, NF Powder for Solution) was approved on 02/18/99 under NDA 20-698. MiraLax contains only one component, PEG3350 powder. It is indicated for occasional constipation in adults and the dosing regimen is 17 grams (one scoopful) QD with 4-8 ounces of water, juice, soda, coffee or tea and the solution is given orally for 14 days or less or as directed by a physician.

On 12/05/05, the sponsor submitted NDA 22-015 for switching MiraLax from prescription to OTC use. No change to the composition for MiraLax OTC is made. Four sizes are packaged, 17, 119, 238, and 527 grams. It is to be indicated for the treatment of occasional constipation with the same dosing recommendation of 17 grams  QD given with 4-8 ounces of water, juice, soda, coffee or tea for 14 days, or less, or as directed by a physician.

In this NDA, four human PK studies were submitted covering single-doses in healthy subjects and multiple-doses in healthy subjects (with normal renal function) and in otherwise healthy subjects with ESRD. Additional PK data from a clinical study in constipated patients (CR3-PK) was also obtained. An *in vitro* hemodialysability of PEG 3350 was also conducted. Per FDA's request, a sensitive LC/MS/MS analytical method was developed and used for determining plasma, urinary, and fecal PEG 3350 levels and its PK data of PEG3350 if absorbed.

The results showed that 1) after multiple oral dosing of 17 g QD x 7 days, mean recovery of PEG 3350 in feces was around 93% or higher in 10 days and 2) 0.12% up to 0.58% of an oral dose of PEG3350 was absorbed following single or multiple doses of PEG3350 to healthy subjects. No major differences were found in the amount of PEG3350 excreted in urine between men and women or between the young and the elderly. Similar exposure was seen between single-dose and multiple-dose PK and that between healthy subjects and constipated patients with normal renal function. Mean terminal  $T_{1/2}$  of PEG3350 was increased from 4-8 hrs (in healthy subjects or patients with normal renal function) to 38.5 hrs in subjects with ESRD (<10 mL/min) with an increased systemic exposure up to 5 fold. Since PEG3350 is not metabolized and once absorbed, it is eliminated solely by excretion through kidneys, an increased  $T_{1/2}$  in subjects with ESRD is as expected (with a corresponding increase in AUC) due to compromised renal excretion function and is unlikely to represent a true increase in absorption. The *in vitro* simulation for hemodialysis estimated that about 30% of PEG3350 was removed during the hemodialysis.

## IV. Question Based Review

### A. General Attributes

On 12/05/05, the sponsor submitted NDA 22-015 for switching MiraLax from prescription to OTC use. No change to the composition for MiraLax OTC is made. Four sizes are packaged, 17, 119, 238, and 527 grams. It is to be indicated for the treatment of occasional constipation and the dosing regimen is 17 grams QD for with 4-8 ounces of water, juice, soda, coffee or tea and the solution is given orally for 14 days, or less, or as directed by a physician.

### B. General Clinical Pharmacology:

The following table summarized all human PK studies conducted in healthy young and elderly (male/female) subjects, otherwise healthy subjects with ESRD, and in constipated patient with normal renal function.

5.2 TABULAR LISTING OF ALL CLINICAL STUDIES

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design And Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	851-PK-001	Volume 4.1 Tab 5.3.3.1A	Evaluate PK of PEG 3350 after a single dose.	Unblinded, no control	MiraLAX 17 g/day oral	6	Healthy Subjects	Single dose	Complete; Full
PK	851-PK-002	Volumes 5.1-5.2 Tab 5.3.3.1B	Evaluate PK of PEG 3350 during 7 days.	Unblinded, no control	MiraLAX 17 g/day oral	14	Healthy Subjects	7 daily doses	Complete; Full
PK	851-PK-004	Volume 7.1 Tab 5.3.3.2A	Examine the effects of end stage renal disease on the PK of PEG 3350.	Unblinded	MiraLAX 17 g/day oral	12	6 patients with end-stage renal disease and 6 matched healthy controls	7 daily doses	Complete; Full
PK	851-PK-005	Volumes 6.1-6.2 Tab 5.3.3.1C	Examine the effects of age on the PK of PEG 3350.	Unblinded, young and elderly adults	MiraLAX 17 g/day oral	12 elderly, 11 young	Healthy Subjects	7 daily doses	Complete; Full
PK	851-CR3-PK	Volume 7.1 Tab 5.3.3.5A	Examine the PK of PEG 3350 in a chronic dosing study	Unblinded, no control	MiraLAX 17 g/day oral	24	Adults with at least three months' history of constipation.	Up to 207 daily doses	Complete; Full

**Q1. As reported, is PEG3350 really not absorbable after oral administration?**

**A1.** With a sensitive LC/MS/MS assay method, the mean fraction of PEG 3350 absorbed was found to be < 0.6% (range: 0.15% to 0.58%) after single and/or repeated oral dosing as shown below.

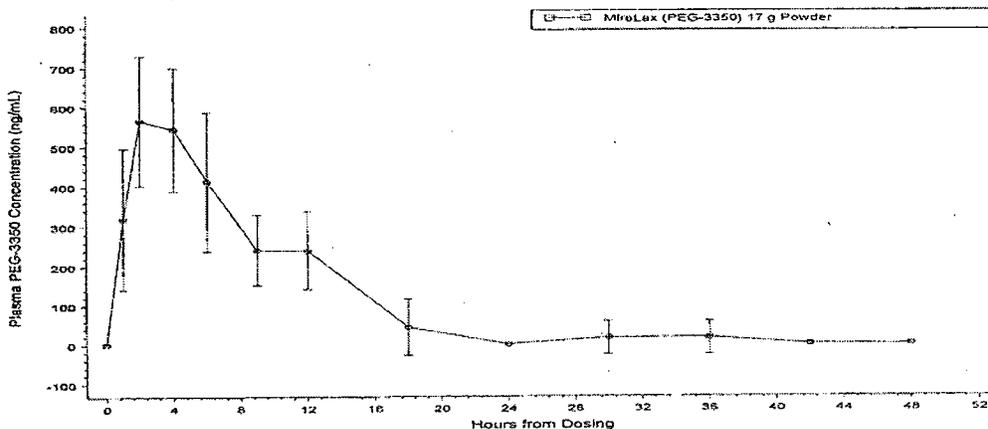
**TABLE 2.7.2-3 RESULTS OF MULTIPLE DOSE HUMAN PHARMACOKINETIC STUDIES.**

Subjects	Adult Humans (< 65 years)	Adult Humans (< 65 years)	Young (18-40 years) Adults	Elderly ≥65 years) Adults	Humans with ESRD	Matched NVs to ESRD
Study #	851-PK-002	851-PK-002	851-PK-005	851-PK-005	851-PK-004	851-PK-004
Location in CTD Module Volume Tab	5 5.1-5.2 5.3.3.1B	5 5.1-5.2 5.3.3.1B	5 6.1-6.2 5.3.3.1C Addendum III	5 6.1-6.2 5.3.3.1C Addendum III	5 7.1 5.3.3.2A	5 7.1 5.3.3.2A
Gender (M/F)/Number	7M/7F	7M/7F	5M/6F	6M/6F	5M/1F	5M/1F
Feeding condition	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation Route	Water/Solution Oral	Water/Solution Oral	Water/Solution Oral	Water/Solution Oral	Water/Solution Oral	Water/Solution Oral
# of Daily Doses	5	7	7	7	7	7
PK parameters:						
Doses (g/kg)	0.20/0.24	0.20/0.24	0.22/0.28	0.22/0.26	0.22	0.20
Males/Females C <sub>max</sub> (ng/mL)	655/914	611/1111	353/542	569/697	3286.2 <sup>a</sup>	1426.8 <sup>a</sup>
T <sub>max</sub> (hrs)	3.71/3.75	5.3/2.9	1.6/1.9	3.0/5.4	T <sub>max</sub> = 3.3 <sup>a</sup>	T <sub>max</sub> = 5.1 <sup>a</sup>
AUC (0-tau) (ng <sup>2</sup> h/mL.)	4650/6314	5226/8738	4751/3947	5309/6108	60858.4 <sup>a</sup>	11082.4 <sup>a</sup>
T <sub>1/2</sub>	3.57/5.26	8.0/6.0	6.6/4.4	5.6/5.3	38.5	4.5
Cum % Dose Excreted in Urine over 24 hours	0.15/0.15	0.30/0.21	0.21/0.24	0.25/0.25	ND	0.58

<sup>a</sup>- Data pooled for males and females

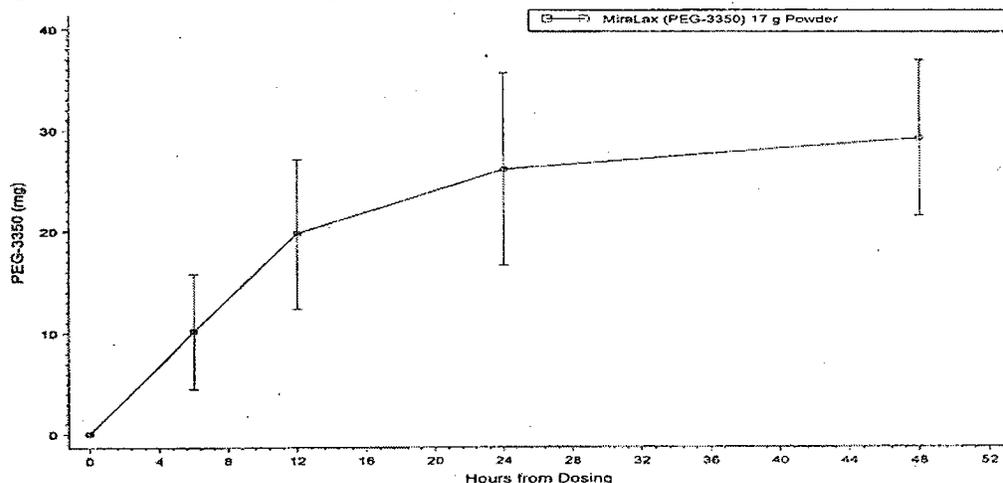
The mean plasma and mean urinary excretion (Ae %) profiles of PEG 3350 after a single dose in healthy subjects (Study No. 851-PK-001) are shown below in Figures 1 and 2:

**Figure 1. Mean Plasma PEG 3350 Levels After Single Dosing of 17 g**



MDS Pharma Services Project AA02332

Figure 2. Mean Urinary Recovery of PEG 3350 After Single Dosing of 17 g



\* = Endpoint Time of the Collection Interval.  
MDS Pharma Services Project AA02332

C. Intrinsic Factors:

Mean terminal  $T_{1/2}$  of PEG3350 was increased from 4-8 hrs (in healthy subjects or constipated patients with normal renal function) to 38.5 hrs in otherwise healthy subjects with ESRD (<10 mL/min) with an increased systemic exposure up to 5 fold. The increased  $T_{1/2}$  in subjects with ESRD is as expected due to compromised renal excretion function and is unlikely due to a true increase in absorption. The *in vitro* simulation for hemodialysis estimated that about 30% of PEG3350 was removed during the hemodialysis.

D. Extrinsic Factors: None

E. General Biopharmaceutics:

MiraLax<sup>®</sup> (Polyethylene Glycol 3350, NF Powder for Solution) contains only one component, PEG 3350 powder.

F. Analytical Section

An LC/MS/MS method was developed and employed for determining the PEG 3350 levels in human plasma (range: █████ ng/mL), urine (range: █████ ng/mL), and feces (range: █████ μg/g). The lower limit of quantification (LLOQ) was 100 ng/mL for plasma sample, 30 ng/mL for urinary sample, and 500 μg/g for fecal sample. The assay method was reviewed and found acceptable. The same HPLC/MS/MS method was also used for determining PEG 3350 levels in dialysate for *In Vitro* Hemodialysability test. The assay validation summary is provided below:

**I. Plasma Samples:**

Standard Curve (n=6)	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL
Accuracy (Bias %)	-3.5% (n=3)	5.6% (n=3)	3.9% (n=3)	0.54% (n=3)	-15% (n=3)	13% (n=3)
Precision (CV%)	10% (n=3)	6.2% (n=3)	9.1% (n=3)	0.93% (n=3)	9.0% (n=3)	8.0% (n=3)

QC Conc. (n=3)	ng/mL	ng/mL	ng/mL
Accuracy (Bias %)	-6.0% (n=3)	-1.1% (n=3)	-12% (n=3)
Precision (CV%)	9.1% (n=3)	5.9% (n=3)	3.7% (n=3)

**II. Urinary Samples:**

Standard Curve (n=7)	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL
Accuracy (Bias %)	2.8% (n=3)	-1.8% (n=3)	-2.6% (n=3)	0.89% (n=3)	3.2% (n=3)	-2.3% (n=3)	0.18% (n=3)
Precision (CV%)	2.2% (n=3)	1.7% (n=3)	0.98% (n=3)	1.9% (n=3)	2.1% (n=3)	2.7% (n=3)	2.3% (n=3)

QC Conc. (n=3)	ng/mL	ng/mL	ng/mL
Accuracy (Bias %)	-0.29% (n=3)	-8.4% (n=3)	-7.6% (n=3)
Precision (CV%)	8.8% (n=3)	0.69% (n=3)	2.1% (n=3)

**III. Fecal Samples:**

Standard Curve (n=5)	µg/g	µg/g	µg/g	µg/g	µg/g
Accuracy (Bias %)	0.55% (n=15)	-0.32% (n=15)	-1.1% (n=15)	2.7% (n=15)	-1.3% (n=15)
Precision (CV%)	4.0% (n=15)	4.5% (n=15)	4.7% (n=15)	4.1% (n=15)	2.8% (n=15)

QC Conc. (n=3)	µg/g	µg/g	µg/g
Accuracy (Bias %)	2.2% (n=9)	0.63% (n=9)	9.3% (n=9)
Precision (CV%)	3.7% (n=9)	2.5% (n=9)	3.3% (n=9)

## **V. Detailed Labeling Recommendations**

The sponsor proposes OTC labeling is acceptable from OCP perspective, however, the PK information obtained from this NDA should be reflected/updated in the current labeling of MiraLax for prescription use as well.

## **VI. Appendices**

- A. Proposed Package Insert (Original and Annotated)
- B. Individual Study Review
- C. Cover Sheet and OCPB Filing/Review Form

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**NDA 22-015 for MiraLax (PEG335) Oral Solution**

**Appendix 1**

**Sponsor Proposed Labeling (12/05/05 Version)**

1   Page(s) Withheld

       Trade Secret / Confidential

  ✓   Draft Labeling

       Deliberative Process

# **NDA 22-015 for MiraLax (PEG335) Oral Solution**

## **Appendix 2**

### **Photo Copies of Synopses of and Sponsor's Comments on Individual Studies**

(Note: Please see OCP final review comments on this NDA)

Braintree Laboratories, Inc.  
MiraLax™ (PEG-3350 NF Powder), Protocol 851-PK1  
MDS Pharma Services Project AA02332

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## REPORT SYNOPSIS

**TITLE:** A Single Dose Pharmacokinetic Evaluation of MiraLax™ (PEG-3350 NF Powder) in Normal Volunteers

**SPONSOR:** Braintree Laboratories, Inc.  
60 Columbian St.  
P.O. Box 850929  
Braintree, MA 02185

**STUDY SITE:** MDS Pharma Services  
Clinical Research  
1930 Heck Avenue – Building 2  
Neptune, New Jersey 07753

**PRINCIPAL INVESTIGATOR:** Magdy Shenouda, MD

**OBJECTIVE:** The objective of this study was to evaluate the pharmacokinetics of a single dose of MiraLax™ in 6 adult volunteers.

**STUDY DESIGN:** This was an unblinded study of the levels of PEG-3350 in urine and blood in healthy adult volunteers receiving a single 17 g oral dose of MiraLax™.

**TREATMENTS:** A. MiraLax™ (Polyethylene Glycol 3350, NF) Powder for Solution  
Manufactured by Braintree Laboratories, Inc.  
Lot No.: 021013  
Expiration date: 30 Sep 2004

Subjects received a single 17 g oral dose of MiraLax™ (polyethylene glycol 3350, NF) powder for solution that was mixed with 250 mL of room temperature water.

PK MEASURES

AND METHODS:

The plasma pharmacokinetic parameters AUC(0-t), Cmax, and Tmax were determined from plasma PEG-3350 concentrations versus time profiles following administration of a single 17 g oral dose of MiraLax™. AUC(0-inf), Kel, and T1/2 could not be calculated from the plasma data due to a limited number of points in the elimination phase. From the urine data, amount excreted, cumulative amount excreted, the cumulative percent of dose excreted (Cum. % Dose), and excretion rate were calculated for each collection interval. In addition, the T1/2 and Kel were calculated from the excretion rate-time data. The percent of dose excreted from time 0 to infinity [Cum. % Dose (0-inf)] was estimated.

RESULTS:

The arithmetic means and standard deviations of PEG-3350 pharmacokinetic parameters following MiraLax™ administration are summarized in the following table.

Summary of PEG-3350 Pharmacokinetic Parameters

Pharmacokinetic Parameters	Arithmetic		
	N	Mean	SD
Cmax (ng/mL)	6	581	158
Tmax (hr)	6	3.04	1.07
AUC(0-t) (ng*hr/mL)	6	4998	1180
T1/2 (hr)	4	5.83	0.686
Kel (1/hr)	4	0.120	0.0134
Cum. % Dose	6	0.172	0.045
Cum. % Dose(0-inf )	4	0.190	0.046

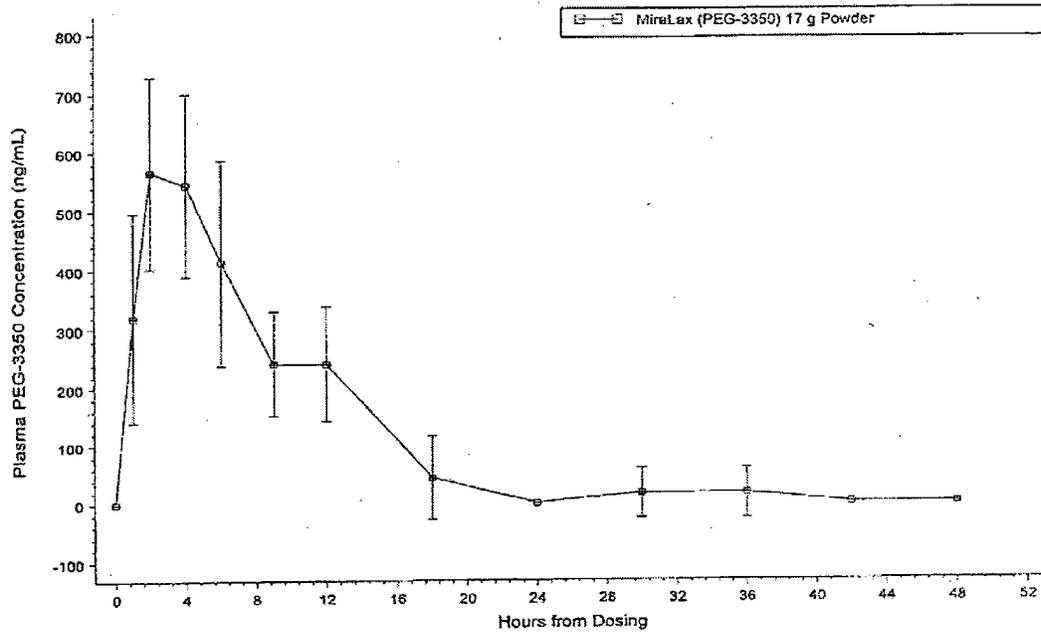
Cum. % Dose = Percent of dose excreted in the urine over 48 hours.

Cum. % Dose (0-inf) = Percent of dose excreted in the urine from time 0 to infinity.

CONCLUSION:

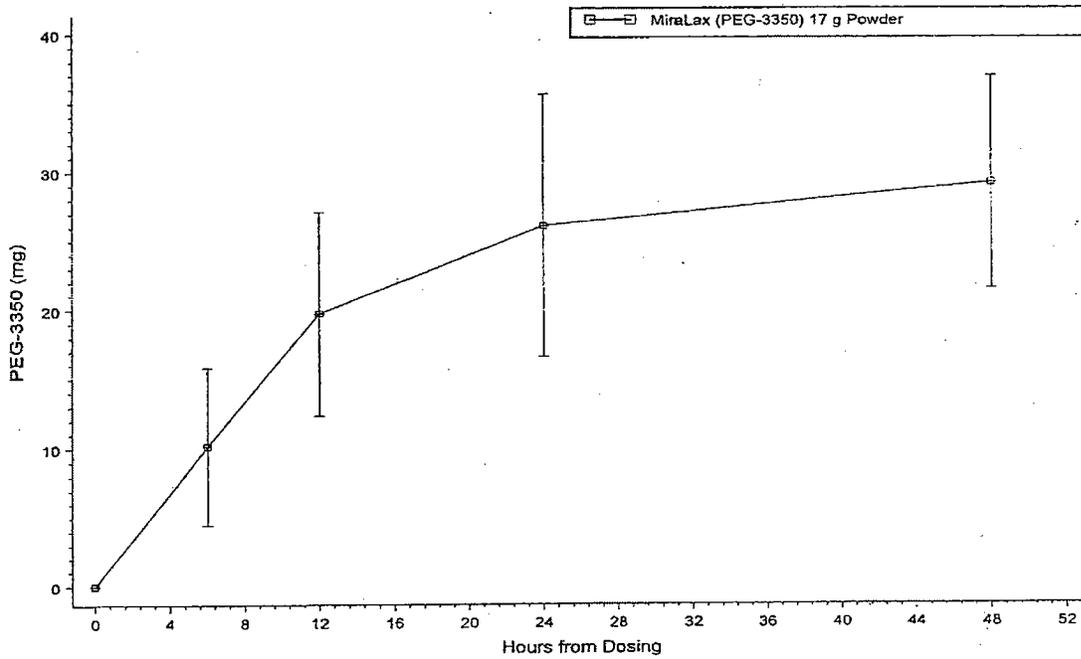
PEG-3350 was poorly absorbed. Mean Cmax and AUC(0-t) following a 17 g dose were 581 ng/mL and 4998 ng\*hr/mL, respectively. The mean percent of dose excreted in the urine over 48 hours was 0.172% in 6 subjects. Based on the data from 4 subjects, 99% of the excretion occurred in 48 hours. On average, the half-life of PEG-3350, derived from urinary excretion data, was 5.83 hours.

**Figure 1. Mean Plasma PEG 3350 Levels After Single Dosing of 17 g**



MDS Pharma Services Project AA02332

**Figure 2. Mean Urinary Recovery of PEG 3350 After Single Dosing of 17 g**



\* = Endpoint Time of the Collection Interval.  
MDS Pharma Services Project AA02332

Braintree Laboratories, Inc.  
MiraLax™ Protocol 851-PK-002  
MDS Pharma Services Project AA03546

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#### REPORT SYNOPSIS

**TITLE:** A Multiple Dose Pharmacokinetic Study of MiraLax™ (PEG-3350 NF Powder) in Normal Volunteers

**SPONSOR:** Braintree Laboratories, Inc.  
60 Columbian St.  
Braintree, MA 02185

**STUDY SITE:** MDS Pharma Services  
Clinical Research  
Neptune, NJ

**PRINCIPAL INVESTIGATOR:** Magdy L. Shenouda, MD

**OBJECTIVE:** The objective of this study was to examine the pharmacokinetics of MiraLax™ in the blood and urine of normal volunteers receiving 17 grams per day of MiraLax™ for 7 days.

**STUDY DESIGN:** This study had an unblinded design.

**TREATMENTS:** A: MiraLax™ (polyethylene glycol 3350, NF powder for solution)  
Manufactured by Braintree Laboratories Inc.  
Lot No.: D21013  
Expiration date: 30 Sep 2004

MiraLax™ (PEG-3350 NF) was provided in 17 gram, single dose packets.

Once a day for 7 days, subjects received a 17 g oral dose of MiraLax™ (PEG-3350 NF) dissolved in 250 mL of water. Subjects were required to wash their hands thoroughly after dosing. This precaution was taken to minimize the possible contamination of the blood collection site or of urine with any MiraLax™ that may have spilled during its consumption.

PK MEASURES

AND METHODS: Plasma and urine were collected on Days 1, 5, and 7 of a 7-day regimen of 17 g MiraLax™ once daily. The plasma pharmacokinetic parameters AUC(0-t), AUC(0-tau), T1/2, Kel, Cmax, and Tmax were determined. Additionally, AUC(0-inf) following the first dose and the accumulation ratio  $[AUC(0-tau)_{Day 7}/AUC(0-tau)_{Day 1}]$  were calculated.

The amount excreted, cumulative amount excreted, the cumulative percent of dose excreted, and excretion rate were calculated from the urine data. In addition, the T1/2 and Kel were calculated from the excretion rate-time data following the dose on Day 7.

Wilcoxon Signed Rank test was used to compare the Cmax, Tmax, AUC, and Cum. Ae(0-24) between the study days (Day 5 versus Day 1, Day 7 versus Day 1, and Day 7 versus Day 5). T1/2 was not compared statistically because the number of subjects with estimable T1/2 values was too low.

RESULTS:

The plasma and urine PEG-3350 data were quite variable and the medians for the pharmacokinetic parameters Cmax, AUC, and Day 7 24-hour amount excreted (Ae) were lower than the means because a few subjects had exceptionally high values. Since the distribution of the data appeared skewed, the median and range data are presented in the summary tables and statistical testing was done using a nonparametric test. The plasma PEG-3350 pharmacokinetic parameters following MiraLax™ administration are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma PEG-3350 for Days 1, 5, and 7

Pharmacokinetic Parameters	Plasma PEG-3350								
	Day 1			Day 5			Day 7		
	N	Median	Range	N	Median	Range	N	Median	Range
Cmax (ng/mL)	14	571	106-1592	14	576	251-2018	14	755	163-2152
Tmax (hr)	14	2.04	0.999-8.08	14	2.00	2.00-9.97	14	2.01	0.991-18.1
AUC(0-t) (ng*hr/mL)	14	2606	110-9482	14	3549	775-9456	14	4702	1234-15518
AUC(0-tau) (ng*hr/mL)	14	3839	867-10292	14	4406	2422-9847	14	5928	2062-16726
T1/2 (hr)	4	4.43	2.88-6.72	7	3.60	3.15-7.36	7	6.60	5.08-9.27
Kel (1/hr)	4	0.165	0.103-0.241	7	0.192	0.0942-0.220	7	0.105	0.0748-0.136

From Day 1 to Day 5, median Cmax values were nearly identical and there was a small increase (< 15%) in median AUC(0-tau).

Median Tmax was 2 hours on both days. Median half-life values were also similar (4.4 and 3.6 hours). There were no significant differences ( $p > 0.05$ ) in Cmax, Tmax, or AUC(0-tau) between Day 5 and Day 1.

From Day 5 to Day 7, median AUC(0-tau) increased 35% and Cmax increased 31%, but the differences were not statistically significant. The lack of a significant difference in AUC(0-tau) between Day 7 and Day 5 indicated that steady state was reached. Median Tmax remained at 2 hours. Median T1/2 was somewhat longer on Day 7 (6.6 hours). The median accumulation ratio (Day 7/Day 1) was 1.7.

The urine PEG-3350 parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Urine PEG-3350 for Days 1, 5, and 7

Pharmacokinetic Parameters	Urine PEG-3350								
	Day 1			Day 5			Day 7		
	N	Median	Range	N	Median	Range	N	Median	Range
T1/2 (hr)	.	.	.	.	.	.	11	6.75	3.17-11.0
Kel (1/hr)	.	.	.	.	.	.	11	0.103	0.063-0.219
Cum. Ae (mg)	14	28.8	4.9-59.6	14	23.2	7.5-61.6	12	31.5	7.3-116.2
Cum. % Dose (%)	14	0.17	0.03-0.35	14	0.14	0.04-0.36	12	0.19	0.04-0.68

Cum. %Dose = The percent of dose excreted over 24 hours.

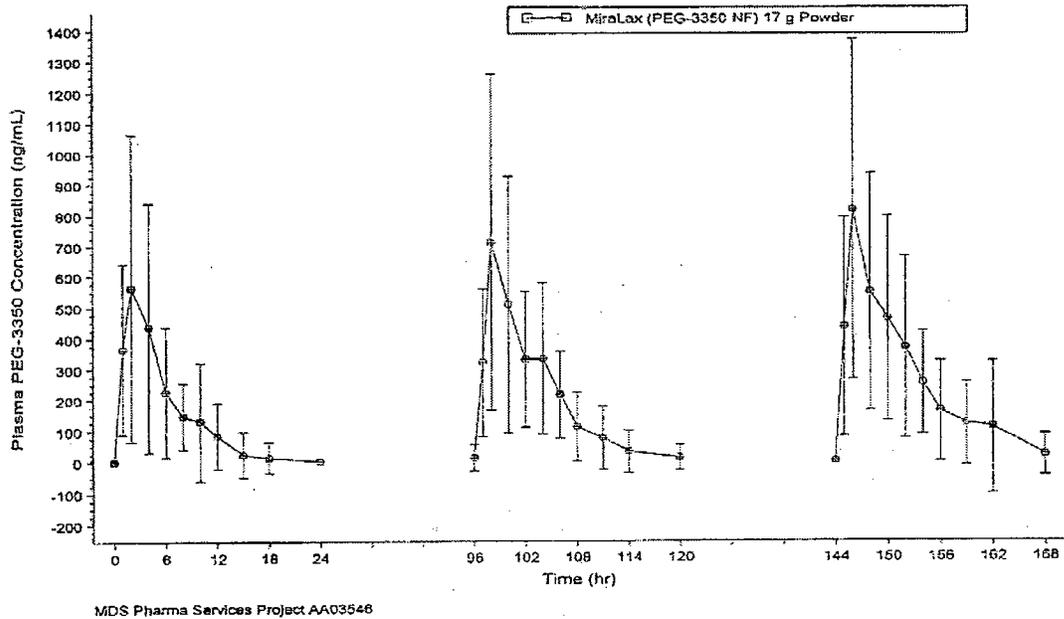
Cum. Ae = The amount excreted over 24 hours.

The urine data were generally consistent with the plasma data. Urine data were similar between Day 5 and Day 1. There was no significant difference in median amount excreted over 24 hours on Day 5 compared to Day 1. From Day 5 to Day 7, median amount excreted over 24 hours increased 36% ( $p = 0.01$ ). However, there was no significant difference in daily amount excreted between Day 7 and Day 1, indicating that there was not a consistent increasing trend. Median half-life following the dose on Day 7 was 6.8 hours.

**CONCLUSION:**

Following once-daily dosing of 17 g MiraLax™ for 7 days, there was no significant difference in PEG-3350 exposure between Day 5 and Day 1. From Day 5 to Day 7, there was a trend of increasing C<sub>max</sub> and AUC(0-tau) but the increases (31%-35%) were not statistically significant. The amount excreted in the urine over 24 hours on Day 7 was 36% higher compared to Day 5; however, there was no significant difference in daily amount excreted between Day 7 and Day 1.

**Figure 1. Mean Plasma PEG 3350 Levels on Days 1, 5, and 7 after Multiple Dosing (17 g QD x 7 Days)**



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Braintree Laboratories Report 851-PK-004  
Pharmacokinetics of PEG 3350 in ESRD Patients and Normal Volunteers

### REPORT SYNOPSIS

**TITLE:** The Effect of Renal Disease on the Multiple Dose Pharmacokinetics of MiraLax™ (PEG 3350 NF Powder) Braintree Protocol 851-PK-004

**SPONSOR:** Braintree Laboratories, Inc.  
60 Columbian St. West  
P.O. Box 850929  
Braintree, MA 02185

**PRINCIPAL INVESTIGATOR:** Suzanne K. Swan, MD  
DaVita Clinical Research  
825 South 8th St, Suite 300  
Minneapolis, MN 55404

**OBJECTIVE:** To examine the effects of renal disease on the pharmacokinetics of PEG 3350 in the blood of patients receiving 17 grams per day of MiraLax™ for 7 days.

**STUDY DESIGN:** This was an unblinded study of the levels of PEG 3350 in blood and in urine in healthy adult volunteers (NV) and in blood in patients with End Stage Renal Disease (FDA Group 5 ESRD) who received 7 days of oral administration of 17 g per day of MiraLax™. Pharmacokinetic (PK) blood and urine sampling were conducted after the 7<sup>th</sup> dose.

**TREATMENT:** MiraLax (Polyethylene Glycol 3350, NF Powder for Solution)  
Manufactured by Braintree Laboratories, Inc.  
Lot No. D4B009.

MiraLax™ laxative, provided in single dose pouches containing 17 g of PEG 3350 was dissolved in 250 mL of water for oral administration to the study subjects.

Braintree Laboratories Report 851-PK-004  
 Pharmacokinetics of PEG 3350 in ESRD Patients and Normal Volunteers

PK MEASURES

AND METHODS: The plasma and urine (in healthy adult volunteers) PEG 3350 concentrations were measured using a validated LC/MS/MS method. For urine and plasma, the Lower Limit of Quantitation (LLOQ) was 30 ng/mL and 100 ng/mL, respectively. The plasma PEG 3350 pharmacokinetic parameters AUC(0-t), AUC(0-tau), T<sub>1/2</sub>, Kel, C<sub>max</sub>, and T<sub>max</sub> were determined from the plasma concentration-time data following 24 hours after the dose on Day 7. The amount excreted, cumulative amount excreted [Cum.Ae(0-24)], the cumulative percent of dose excreted, excretion rate, and renal clearance (CL<sub>r</sub>) of PEG 3350 were calculated from the urine data following the dose on Day 7.

RESULTS: PEG 3350 analyses were performed in 12 patients, 6 (5 males) with ESRD and 6 age, weight, and gender matched controls. Plasma levels ranged from [redacted] ng/mL and were significantly elevated in ESRD patients compared to normal volunteers. AUC and T<sub>1/2</sub> were significantly higher in ESRD patients compared to the healthy volunteers, while T<sub>max</sub> did not differ. Whereas plasma levels prior to dosing were < LLOQ in all normal volunteers and were < LLOQ in 5/6 of them at 24 hours after dosing, PEG 3350 was detectable in ESRD patients prior to dosing and for up to 48 hours after dosing. The following table summarizes the pharmacokinetic parameters observed after 7 daily doses of MiraLax.

Treatment Group	Pharmacokinetic Parameter*			
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC (0-tau) ng*hr/mL	T <sub>1/2</sub> (hr)
ESRD Patients (N=6)	3286.2 (1664.1)	3.33 (1.99)	60858.4 (36653.4)	38.5 (22.6)
Healthy Volunteers (N=6)	1426.8 (807.1)	5.1 (5.6)	11082.4 (7161.9)	4.5 (2.6)
P value**	0.005	0.90	0.0002	0.004

\* Values are means and (SD). \*\* Calculated from the weight adjusted ln-transformed data.

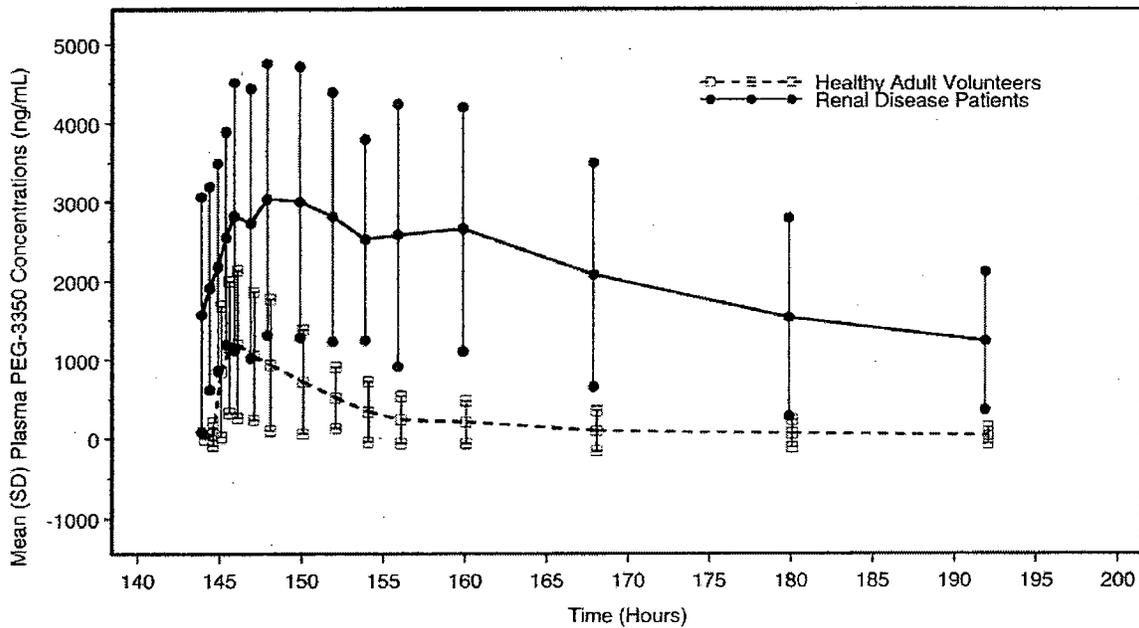
The mean pre-dose levels before the fifth daily dose in ESRD patients did not differ from the pre-dose levels before, or 48 hours after the seventh dose.

Urinary PEG 3350 concentrations in healthy adult volunteers ranged from  $\text{---} \mu\text{g/mL}$  to  $\text{---} \mu\text{g/mL}$ . The mean cumulative amount of the administered dose that was excreted in urine in the first 24 hours after dosing on Day 7 was 0.58%.

**CONCLUSION:**

Plasma concentrations in normal healthy adults and patients with ESRD were variable. ESRD patients experienced higher exposures. However, plasma PEG 3350 levels pre-dose during the interdialytic level, before the final dose, and 48 hours after the final dose were similar, suggesting that there was no additional accumulation of PEG 3350 in plasma following repeated doses. A single dialysis session (as observed from one protocol violator) appears to clear partially plasma PEG 3350.

**Figure 1. Mean Plasma PEG 3350 Levels After Multiple Dosing (17 g QD x 7 Days) to Healthy Subjects and Subjects with End Stage Renal Disease (ESRD)**



Renal Disease Patients are shifted to the left for ease of reading.

Pre-Dose Day 6 was used for ESRD patient #1, who was dialyzed by mistake on Day 7 after dosing.

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## REPORT SYNOPSIS

**TITLE:** An Open-Label, Multiple-Dose Study to Assess the Effect of Age on The Plasma and Urine Pharmacokinetics of MiraLax™ (PEG-3350 NF Powder) in Healthy Adult Subjects

**SPONSOR:** Braintree Laboratories, Inc.  
Braintree, Massachusetts 02185

**STUDY SITE:** MDS Pharma Services  
Clinical Research  
Phoenix, Arizona 85044

**PRINCIPAL INVESTIGATOR:** Mark J. Allison, MD

**OBJECTIVES:** The primary objective of the study was to assess the effect of age on the plasma and urine pharmacokinetics of MiraLax™ following multiple-dose administration to healthy subjects.

The secondary objective of the study was to evaluate the excretion of MiraLax™ via the feces in subjects  $\geq 18$  and  $\leq 40$  years of age.

**STUDY DESIGN:** This study had a single-center, open-label, multiple-dose design.

**TREATMENT:** A/B: MiraLax™ (polyethylene glycol 3350, NF powder for solution) 17 g  
Manufactured by Braintree Laboratories, Inc.  
Lot No.: D4B009  
Expiration date: February 2006

All subjects received a single, pre-weighed, oral dose of approximately 17 g of MiraLax™ (PEG-3350 NF) powder dissolved in 250 mL of tap water by the study staff once daily, at approximately the same time of day for 7 days. Young subjects were designated as Treatment Group A and elderly subjects were designated as Treatment Group B.

Subjects and study personnel were required to wash their hands thoroughly immediately after administration of PEG-3350. In light

of the expected low concentrations of the test article in plasma and urine, this precaution was taken to minimize the risk of contaminating biological samples with the test article.

**PK MEASURES  
AND METHODS:**

Plasma and urine were collected on Day 1 (predose only) and Day 7 of the 7-day regimen of 17 g MiraLax™ once daily in young (Group A) and elderly (Group B) subjects. The plasma PEG-3350 pharmacokinetic parameters AUC(0-t), AUC(0-tau), T1/2, Kel, Cmax, Cmin, and Tmax were determined from the plasma concentration-time data following the dose on Day 7.

The amount excreted, cumulative amount excreted [Cum.Ae(0-24)], the cumulative percent of dose excreted, excretion rate, and renal clearance (CLr) of PEG-3350 were calculated from the urine data following the dose on Day 7.

A general linear model (GLM) was applied to the ln-transformed Cmax, AUC(0-t), AUC(0-tau), Cum. Ae(0-24), and CLr. The Cmax, AUC, and CLr parameters were normalized for body weight prior to log transformation. The least-squares means (LSM), 90% confidence interval (CI), %mean ratio, and p-value ( $\alpha = 0.05$ ) were presented for the comparison between age groups. The Wilcoxon Rank Sum test was used to compare the T1/2 and Tmax between the age groups.

The PEG-3350 amount excreted, cumulative amount excreted, and the cumulative percent of dose excreted in the feces were determined in young subjects at 24-hour intervals from Days 1 through 11.

RESULTS: The PEG-3350 pharmacokinetic parameters and statistical results for young and elderly subjects are presented in the following table.

**Summary of the Pharmacokinetic Parameters of PEG-3350**

Pharmacokinetic Parameters	Elderly Subjects			Young Subjects			% Mean Ratio*	90% CI*	P-Value*
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD			
Cmax (ng/mL/kg)	12	9.31	5.39	11	6.89	3.68	134.9	84.12 - 216.48	0.2875
AUC(0-t) (ng*hr/mL/kg)	12	66.73	40.85	11	39.68	26.32	210.3	100.12 - 441.80	0.0995
AUC(0-tau) (ng*hr/mL/kg)	11	83.05	39.84	7	64.33	20.46	121.0	84.32 - 173.73	0.3701
CLr (mL/min/kg)	12	1.88	0.62	10	2.77	0.83	80.5	64.36 - 100.65	0.1095
Cum. Ae(0-24) (mg)	12	41	14	13	37	17	115.0	85.11 - 155.51	0.4321
Cum. %Dose(0-24)	12	0.25	0.08	11	0.23	0.10	-	-	-
Tmax (hr) **	12	2.02	2.00 - 4.03	11	2.00	1.00 - 2.05	-	-	0.0604
T1/2 (hr)	11	5.55	1.52	7	5.00	2.13	-	-	0.2771
Cum. Ae(0-240) (g)	-	-	-	11	108.25	29.84	-	-	-
Cum. %Dose(0-240)	-	-	-	11	93.29	25.70	-	-	-

\* From the ANOVA. P-Values for Tmax and T1/2 are from the Wilcoxon Rank Sum Test.  
\*\* Median and Range are presented for Tmax.

Cum. Ae(0-24): Cumulative amount excreted in the urine from 0-24 hours relative to Dose 7.  
Cum. %Dose(0-24): Cumulative % of dose excreted in the urine from 0-24 hours relative to Dose 7.  
Cum. Ae(0-240): Cumulative amount excreted in the feces from 0-240 hours relative to Dose 1.  
Cum. %Dose(0-240): Cumulative % of dose excreted in the feces from 0-240 hours relative to Dose 1.

Source: Tables 5, 6, 8, 9, 12, 13 and 14

There were no statistically significant differences in the PEG-3350 plasma and urine pharmacokinetic parameters between the elderly and young subjects ( $p > 0.05$  for all parameters). The differences in the exposure parameters between elderly and young were not statistically significant. Mean total PEG-3350 exposure, based on geometric mean AUC(0-tau) from the ANOVA, was 21% higher in the elderly. Mean total exposure based on AUC(0-t) was approximately 2-fold higher in the elderly. The greater difference in AUC(0-t) was due to one subject in the young group with almost no systemic absorption of PEG-3350. Mean peak exposure (Cmax) was 35% higher in the elderly. PEG-3350 exposure was highly variable, with considerable overlap in individual parameter values between the two groups.

Mean cumulative excretion over 24 hours [Cum. Ae(0-24)] and mean renal clearance of PEG-3350 based on geometric means were similar (difference of  $\leq 20\%$ ) in the two groups and no statistically significant differences were found. The cumulative % of the

administered dose excreted in urine did not differ between young (0.23%) and elderly (0.25%) subjects.

The mean plasma half-life of PEG-3350 was approximately 5 hours in both groups and no significant difference was shown. Median T<sub>max</sub> (2 hours) was also not different between the two groups.

In 8 of 12 elderly subjects, the estimated creatinine clearance ranged from 50 to 80 mL/min, which is classified as mild renal impairment by FDA criteria (FDA Group 2 Mild Kidney Impairment).<sup>1</sup> All subjects had a serum creatinine within the lab normal range of 0.5 to 1.3 mg/dL at screening. Therefore, the lower creatinine clearance values for the elderly can be considered to be due to age-related decline in renal function. Despite the lower creatinine clearance, no relationship between PEG-3350 exposure and renal function was observed.

In the young subjects, an average of 93% of the total PEG-3350 dose was excreted in the feces over the 10-day measurement period. In 6 of 11 subjects, approximately 100% of the administered dose was recovered in feces within 4 days of the last dose.

**CONCLUSIONS:** There was no statistically significant difference in systemic exposure of PEG-3350 between the elderly and young subjects. Both exposure parameters (C<sub>max</sub> and AUC) were highly variable and values exhibited substantial overlap between the two groups.

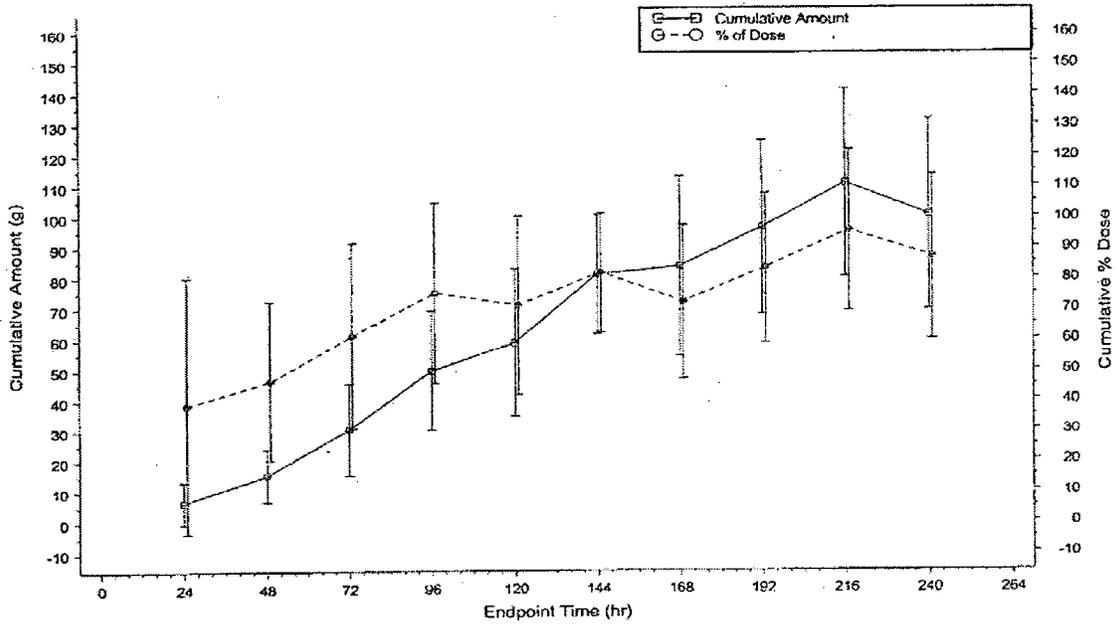
There was no statistically significant difference in PEG-3350 renal clearance between the elderly and young subjects. Although mean renal clearance of PEG-3350 trended lower in elderly subjects, substantial variability and overlap in individual values between the two groups was observed. Despite the fact that most of the elderly subjects had FDA Group 2, Mild Kidney Impairment, there was no apparent relationship between PEG-3350 systemic exposure and creatinine clearance.

There was no difference in cumulative amount or % of dose excreted in the urine, plasma T<sub>max</sub>, or T<sub>1/2</sub> between the elderly and young subjects.

Consistent with previous findings, PEG is minimally absorbed. It is excreted predominately in the feces where nearly 100% was recovered in 6 of the 11 subjects within 4 days of cessation of dosing. Approximately only 0.25% of the administered dose is excreted in urine.

On average, 93% of the dose was excreted in the feces in the young subjects.

**Figure 1. Mean Fecal Recovery (0 - 240 hr) of PEG 3350 in Subjects After Multiple Dosing (17 g QD x 7 Days)**



% of Dose is shifted to the right for ease of reading.  
Last dose was administered at Hour 144.  
MDS Pharma Services Project AA18286  
Program: DM\_P11:HLAA18286A.PKSAS\MEANGRAPH-FECAL-NEW.SAS 25JAN2005 14:50

**Appears This Way  
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**IN VITRO EVALUATION OF THE HEMODIALYZABILITY OF  
POLYETHYLENE GLYCOL 3350:  
BRAINTREE LABORATORIES PROTOCOL PK-006**

**Abstract:**

Background: Hemodialysis (HD) and hemofiltration (HF) are forms of renal replacement therapy (RRT) for patients with kidney failure. Estimating the extent of drug removal under different conditions of RRT (e.g. changes in dialyzer, HD vs HF) presents a challenge when predicting drug elimination and dosage regimen design during these procedures. Evaluation of drug removal based on clinical pharmacokinetic studies in patients receiving RRT is not practical given the increasing number of dialyzers with variable rates of drug removal. *In vitro* dialysis techniques have been developed that allow characterization of drug removal under varying conditions of RRT. Polyethylene Glycol 3350 (PEG 3350 NF for solution, Braintree Laboratories) is a drug for which information on removal by RRT is not available. This study was designed to evaluate the *in vitro* clearance of PEG by three dialyzers of varying composition and under varying conditions of HD and HF.

Methods:

Results:

Conclusion: PEG was removed by the dialyzers tested with the diffusive component contributing to the majority of its removal. To fully assess the overall contribution of dialysis to PEG removal other pharmacokinetic parameters for PEG are required (e.g. non-dialysis clearance).

Braintree Laboratories Report 851-CR3-PK  
Population Pharmacokinetics Study in Braintree Protocol 851-CR3

### REPORT SYNOPSIS

**TITLE:** An Experimental Population Pharmacokinetics Screen of MiraLax™ (PEG-3350 NF Powder) in Patients Participating in

Braintree Protocol 851-CR3: AN OPEN LABEL STUDY OF CHRONIC MIRALAX  
USE IN CONSTIPATED PATIENTS.

**SPONSOR:** Braintree Laboratories, Inc.  
60 Columbian St.  
P.O. Box 850929  
Braintree, MA 02185

**MEDICAL  
MONITOR**



**OBJECTIVE:** The objective of this study was to evaluate the plasma and urinary concentrations of PEG 3350 in constipated patients.

**STUDY DESIGN:** This was a population pharmacokinetic screen of the levels of PEG-3350 in plasma and urine in a subset of constipated adult patients participating in an open label, multicenter safety study of MiraLax at a nominal daily oral dose of 17 grams for up to 12 months.

**TREATMENTS:** A. MiraLax (Polyethylene Glycol 3350, NF)  
Powder for Solution  
Manufactured by Braintree Laboratories, Inc.  
Lot No.: RC1201N7WA.

Subjects received a daily 17 g oral dose of MiraLax™ (polyethylene glycol 3350, NF) powder for solution that was mixed with 8 ounces (240 mL) of water, coffee, tea, juice, or soda.

Braintree Laboratories Report 851-CR3-PK  
Population Pharmacokinetics Study in Braintree Protocol 851-CR3

PK MEASURES

AND METHODS: The plasma and urine PEG-3350 concentrations as related to age, race, gender, time since last dose and duration of dosing were measured using a validated LC/MS/MS method. For urine and plasma, the Lower Limit of Quantitation (LLOQ) was  $\blacksquare$  ng/mL and  $\blacksquare$  ng/mL, respectively.

RESULTS:

PEG 3350 analyses were performed in 24 patients, 10 males and 14 females who took MiraLax for a median duration of 119 days (range 42-207 days). Together they provided 63 plasma and 55 urine samples. Plasma levels ranged from  $\blacksquare$  ng/mL. All plasma levels were within the range seen in formal single and multiple dose pharmacokinetic studies. Plasma levels were < LLOQ in 37/63 samples. They were generally higher in the first 9 hours after dosing, higher in males, and in patients over 65 years of age. Urine PEG-3350 concentrations ranged from  $\blacksquare$  ng/mL. Only one of 55 urine samples had a concentration of PEG 3350 higher than those seen in formal single and multiple dose pharmacokinetic studies. By inspection of the data it was evident that there were no statistically significant effects of demographic parameters on PEG levels in plasma or urine.

CONCLUSION:

Plasma and urine concentrations in constipated adults who took MiraLax daily for up to 207 days were variable. Except for one urine sample, they were within the range seen in formal single and multiple dose pharmacokinetic studies.

# **NDA 22-015 for MiraLax (PEG335) Oral Solution**

## **Appendix 3**

### **OCP Filing/Review Form**

# Office of Clinical Pharmacology

## New Drug Application Filing and Review Form

<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22-015 (RX to OTC Switch)	Brand Name	Miralex	
OCPB Division (I, II, III)	DCP III	Generic Name	PEG3350	
Medical Division	GI	Drug Class	Laxative	
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Occasional constipations	
OCPB Team Leader	Dennis Bashaw Pharm.D.	Dosage Form	Powder for oral solution	
		Dosing Regimen	17 gm per day x 14 days	
Date of Submission	12/08/05	Route of Administration	Oral	
Estimated Due Date of OCPB Review	08/01/06	Sponsor	Braintree	
Medical Division Due Date	08/08/06	Priority Classification	3S	
PDUFA Due Date	10/08/06			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	2	2	
Patients-				
single dose:				
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	1	1	<i>In vitro hemodialysis</i>
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X			
renal impairment:	X			

hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:	X	1	1	Screening only/no actual PPK data analyzed
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CP Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		6	6	
Filability and QBR comments				
	"X" if yes	<i>Comments</i>		
<b>Application filable ?</b>	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>	<b>Are plasma levels of PEG3350 measurable that warrant the drug-drug interaction studies?</b>			
<b>Other comments or information not included above</b>	<b>An OTC Advisory Committee meeting is expected in July/August, 2006.</b>			
<b>Primary reviewer Signature and Date</b>	<b>Tien-Mien Chen/ 01/26/06</b>			
<b>Secondary reviewer Signature and Date</b>				

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

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Tien-Mien Chen  
8/17/2006 09:32:08 AM  
BIOPHARMACEUTICS

Dennis Bashaw  
8/17/2006 02:56:39 PM  
BIOPHARMACEUTICS