CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-015

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-015
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	December 8, 2005
PRODUCT:	Miralax (Polyethylene Glycol 3350 or PEG 3350 Powder for Oral Solution (Rx-to-OTC Switch)
INTENDED CLINICAL POPULATION:	Patients suffering from occasional constipation
SPONSOR:	Braintree Laboratories, Inc.
DOCUMENTS REVIEWED:	Vol. 1.1-1.69
REVIEW DIVISION:	Division of Gastroenterology Products (HFD-180)
PHARM/TOX REVIEWER:	Tamal K. Chakraborti, Ph.D.
PHARM/TOX SUPERVISOR:	Jasti B. Choudary, B.V.Sc., Ph.D.
DIVISION DIRECTOR:	Brian H. Harvey, M.D., Ph.D.
PROJECT MANAGER:	LCDR Keith Olin

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations:

A. Recommendation on approvability: From a preclinical standpoint, this NDA may be approved.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: The sponsor may be asked to modify the proposed label of Miralax PEG 3350 as suggested in the text of this review.

II. Summary of nonclinical findings:

A. Brief overview of nonclinical findings: The systemic toxicity of Miralax PEG 3350 was adequately evaluated in complete range of acute, subacute/subchronic and chronic toxicity studies in mice, rats and dogs. Chronic oral toxicity studies were conducted in rodent (rats up to 6 g/kg/day) up to six months (rats) duration and in non-rodent (dogs) up to nine months (up to 3 g/kg/day) duration. The potential genotoxicity of Miralax PEG 3350 was examined in an adequate battery of genotoxicity tests. The carcinogenic potential of Miralax PEG 3350 has also been examined in CD-1 mice and (104-week) and Sprague Dawley rats (104-week). In addition, Miralax PEG 3350 has been evaluated for fertility and reproductive performance (Segment I) in rats, teratology (Segment II) in rats and rabbits and peri- and post-natal development (Segment III) in rats. Adequate safety pharmacology studies were also conducted with Miralax PEG 3350.

The target organs of toxicity appeared to vary across species. The major target organ of toxicity in the rat appeared to be the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in males at 6 g/kg/day). In dogs, following oral administration of Miralax PEG 3350 for 28-days, the target organs of toxicity appeared to be the lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes; foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates), gastrointestinal tract (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue in females at 3, 6 and 9.3 g/kg/day), testes (hypospermia in the epididymides and seminiferous tubule degeneration or multiucleated spermatids of the testes) and salivary gland (atrophy). Following 9-month oral administration of Miralax PEG 3350 in dogs (up to 3 g/kg/day), the target organs of toxicity appeared to be testes (retarded

development) and prostate (lymphocyte infiltrate) in the males and mammary gland (glandular hyperplasia), liver (vacuolation) and gallbladder (lymphocyte infiltrate and epithelial hyperplasia) in females.

Miralax PEG 3350 was negative in the Ames test and did not show any clastogenic potential in the chromosome aberration test with human peripheral blood lymphocytes. It was also negative in *in vivo* oral rat micronucleus test. In addition, Miralax PEG 3350 was not tumorigenic in mice and rats up to 6 g/kg/day.

In reproductive toxicity studies in rats and rabbits by oral route, Miralax PEG 3350 did not appear to cause any significant adverse effects on the reproductive parameters in either sex. Miralax PEG 3350 did not appear to be teratogenic in rats and rabbits at the tested doses. Miralax PEG 3350 did not cause any effect on pre-and post-natal development in rats up to 2 g/kg/day.

In conclusion, the non-clinical studies conducted with Miralax PEG 3350 adequately support its use at the intended therapeutic dosage and in accordance with the proposed product labeling.

B. Pharmacologic activity: The sponsor did not submit any pharmacology study report. From the published literature, PEG 3350 acts as an osmotic laxative. As a result of its almost total fecal excretion and its osmotic effects within the colon, it increases stool mass and volume. The increased colonic bulk appears to stimulate peristalsis. In addition, its action as a surfactant may improve stool passage. PEG 3350 increased fecal dry and wet weight, fecal water output and fecal volume. It thereby produced a laxative effect consisting of softer, easier to pass stool, with increased stool frequency and water content. PEG 3350 did not appear to affect electrolyte balance.

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-015
Review number: 001
Sequence number/date/type of submission: 000/December 6, 2005/Original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Braintree Laboratories, Inc., Braintree, MA
Manufacturer for drug substance: [redacted]

Reviewer name: Tamal K. Chakraborti, Ph.D.
Division name: Division of Gastroenterology Products
HFD #: 180
Review completion date: July 7, 2006

Drug:

Trade name: Miralax OTC (Over the Counter)
Generic name: Polyethylene glycol (PEG) 3350, NF Powder for Oral Solution
Code name: None
Chemical name: Poly(oxy-1,2-ethanediyl), *alpha-hydro-omega*-hydroxy
CAS registry number: 25322-68-3
Molecular formula/molecular weight: $HO(C_2H_4O)_{75}C_2H_4OH/3350$
Structure: Not available

Relevant NDA: 20-698 (Miralax, Braintree Laboratories, Inc., HFD-180)

Drug class: Laxative

Intended clinical population: Miralax PEG 3350 is intended to be administered in patients suffering from occasional constipation.

Clinical formulation: The drug product is composed of only one component, PEG 3350, NF. The average dose is 17 grams of PEG 3350 powder per day in 4-8 ounces of water, juice, soda, coffee or tea.

The drug product is packaged in a [redacted] container with a [redacted] closure. The container closure system has a foil temper evident induction seal. It is also packaged in unit dose foil pouches. The following four package sizes are intended for distribution: 7 oz container (fill of not less than 119 g), 14 oz container (fill of not less than 238 g), 26 oz container (fill of not less than 527 g), and unit dose foil pouches (fill of not less than 17 g).

Route of administration: Oral (powder for oral solution)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: The following table shows the studies reviewed within this submission.

STUDY	REPORT/ STUDY NO.	TEST SITE	LOT NO.	REV. PAGE
PHARMACOLOGY				7
ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION				11
Oral pharmacokinetic and absorption/elimination study in rats	[redacted] 382008	1	1275	12
Absorption, metabolism, and excretion of ^{14}C-PEG 3350 following oral administration to rats	[redacted] 7496-100	2	1275	13
TOXICOLOGY				17
Acute				19
Rat				19
Oral	[redacted] 382017	1	1275	19
Subacute/Subchronic/Chronic				21
Mouse				21
3-Month, oral	[redacted] 382011	1	1275	21
Rat				27
3-Month, oral	[redacted] 95027	1	222609	27
6-Month, oral	[redacted] 382009	1	1275	31
Dog				37
28-Day, oral	[redacted] 382005	1	1275	37
9-Month, oral	[redacted] 382012	1		42
GENOTOXICITY				48
In Vitro				48
Ames test	21570	3	1275	48
Chromosome aberration assay in human peripheral blood lymphocytes	21899	3	1275	50
In Vivo				53
Oral bone marrow micronucleus test in rats	21736	3	1275	53
CARCINOGENICITY				55
104-Week, oral, mice	[redacted] 382018	1	1274, 1275	55
104-week, oral, rats	[redacted] 382009	1	1275	81
REPRODUCTIVE TOXICITY				110
Rat				110
Segment I, oral	[redacted] 382015	1	1275	110
Segment II, oral	[redacted] 382013	1	1275	113
Segment III, oral	[redacted] 382023	1	1275	124
Rabbit				117
Segment II, oral	[redacted] 382014	1	1275	117

Studies not reviewed within this submission: Analytical methods and validation reports were not reviewed, as these are reports of method development and validation.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The sponsor did not submit any pharmacology study report. From the published literature, PEG 3350 was considered pharmacologically inert. It acts as an osmotic laxative. As a result of its almost total fecal excretion and its osmotic effects within the colon, it increases stool mass and volume. The increased colonic bulk appears to stimulate peristalsis. In addition, its action as a surfactant may improve stool passage.

2.6.2.2 Primary pharmacodynamics

The sponsor stated that studies on the primary pharmacodynamics of Miralax PEG 3350 were not required by the Agency as per Type C Meetings held on September 28, 1999 and on September 6, 2000. However, the sponsor presented reviews of some of the key published literature on PEG 3350, which are discussed below.

PEG 3350 increased fecal dry and wet weight, fecal water output and fecal volume, (Schiller LR et al., 1988. Gastroenterology 94: 933-41; Hammer HF et al., 1989. J Clin Invest 84: 1056-62). It thereby produced a laxative effect consisting of softer, easier to pass stool, with increased stool frequency and water content [Chaussade S, 1999. Ital J Gastroenterol Hepatol 31(Suppl. 3): S242-244]. Since it was not metabolized, PEG 3350 provided no intestinal gas in comparison to that produced by metabolizable laxatives such as lactulose (Attar et al., 1999. Gut 44: 226-30) and certain fibers [Corazziari E, 1999. Ital J Gastroenterol Hepatol 31(Suppl. 3): S232-233]. Unlike sodium phosphate laxatives, PEG 3350 did not appear to produce shifts in clinical chemistry or electrolyte balance (Attar A et al., 1999. Gut 44: 226-230).

Effect on Gastric Motility

PEG 3350 increased fecal dry and wet weight, fecal water output and fecal volume, without increasing the percent of fecal water and thereby stimulated gastrointestinal motility. This was considered an indirect effect of PEG 3350 and was not considered to be mediated via stimulation of the gastric enteric neurons [Tonini M, 1999. Ital J Gastroenterol Hepatol 31(Suppl. 3): S238-241]. PEG 3350 (15 mM) showed no effect on electrically stimulated contractions of longitudinal or circular segments of isolated distal colon muscle strips from rabbits. However, when PEG 3350 solution was instilled directly into the lumen of intact segments of distal colon, an increase in the duration of the peristaltic waves was seen, without increases in their peak amplitude or frequency, in comparison to the response with saline. Addition of muscarinic or tachykinin receptor blockers attenuated this response, suggesting a neuronal involvement.

2.6.2.3 Secondary pharmacodynamics

The sponsor produced reviews some of the key published literature regarding the secondary pharmacodynamics of PEG 3350, which are discussed below.

Pegylation of Proteins

When PEGs were conjugated to proteins, it reduced their renal filtration resulting in the prolongation of their half life in the blood, and reduced potential immune or allergic reactions (Veronese FM, 2001. Biomaterials 22: 405-17). Several "pegylated" drugs are currently available in the market. However, most of the PEGs used for this purpose were high molecular weight PEGs e.g., PEG 5000, PEG 12000 and PEG 20000.

Membrane Sealing Effects

High concentrations (50%) of PEGs and related polymers have been found to seal crushed spinal cord neurons in animals (Borgens RB et al., 2004. J Neurosci Res 76: 141-54). This partially restored anatomical connections, neuronal conduction and promoted recovery of a spinal cord mediated reflex (Borgens RB et al., 2004. J Neurosci Res 76: 141-54). The mechanism was considered to be entirely a mechanical effect on axonal membranes. Biochemical changes associated with repair, e.g., free-radical scavenging or superoxide inhibition, was not observed with PEG. Similar results were observed when PEG 1800 was directly applied to the crushed spinal cord.

2.6.2.4 Safety pharmacology

Renal effects: [redacted] Braintree conducted safety assessment of the effect of single oral doses of Miralax on renal function in dogs as per the Agency recommendation.

Safety Assessment of Miralax PEG3350 on Renal Function Following Single Oral (Gavage) Administration to Dogs (Study No. -382003)

Methods: The objective of this study was to determine the effect of MiraLax PEG-3350 on renal function following single oral (gavage) administration to dogs. In this study, MiraLax™ PEG-3350 was administered via oral gavage once at dosage levels of 6, 12 and 24 g/kg (Groups 2-4). The animals were then maintained for a 48-hour 8 post-treatment period. A concurrent control group (Group 1) received the vehicle (deionized water). Each group consisted of three males and three females. The study design is shown in the table (from page 18 of the study report) below.

Group Number	Test Article	Dosage Level (g/kg)	Concentration (g/mL)	Dosage Volume Water (mL/kg)	Total Dosage Volume (mL/kg)	Number of Animals Males	Females
1	Vehicle	0	0	38.71	38.71	3	3
2	MiraLax™ PEG-3350	6	0.15	33.98	38.71	3	3
3	MiraLax™ PEG-3350	12	0.31	29.18	38.71	3	3
4	MiraLax™ PEG-3350	24	0.62	19.03	38.71	3	3

The animals were observed twice daily for mortality and moribundity. Clinical observations were performed immediately after treatment, approximately two and four hours following dosing, and once daily thereafter. Detailed physical examinations were conducted on a weekly basis and on the last day of the study (study day 2). Body weights were recorded weekly prior to dosing and on study days-1 through 2. Water consumption was recorded daily for study days -2 through 2. Blood for serum chemistry evaluations were collected prior to the initiation of dosing (study day - 1) and on study days 1 and 2. Urine was collected for 24 hours prior to dosing and continuously for 48 hours following dose administration (Period 1: 24 hours baseline, study days -2 to -1; Period 2: 0-3 hours postdose; Period 3: 3-6 hours postdose; Period 4: 6-12 hours postdose; Period 5: 12-24 hours postdose; Period 6: 24-36 hours postdose; Period 7: 36-48 hours postdose). Renal function was assessed by evaluating the following parameters: glomerular filtration rate (GFR), which was approximated by the creatinine the clearance rate, tubular reabsorption (specifically sodium ions), which was reflected in the fractional excretion of sodium, and distal and convoluted tubular regulation of free water reabsorption, which was indicated by the free water clearance.

Results:

There was no treatment-related mortality. Treatment-related clinical signs included emesis (white foamy material) and diarrhea. Dose-related emesis was observed up to 4 hours postdose. Dose-related diarrhea was seen up to 4 hours at all dose levels. There were no treatment-related effects on body weight and water consumption. There were no treatment-related serum chemistry changes except for mean sodium concentration which was significantly increased at 12 and 24 g/kg doses on Day 1. Diuresis was observed in all treated animals.

Urine Quantitative Parameters

Specific gravity was significantly higher for all doses at periods 2 and 3 compared to vehicle-control and at periods 4 and 5 for the 12 g/kg and at period 4 for the 24 g/kg group. The urine volumes were significantly reduced for periods 2 (6 and 12 g/kg doses), 4 (12 g/kg and 5 (12 and 24 g/kg doses) compared to control. In addition, at 2 g/kg dose, significant elevation in the urine pH was observed at period 2. A significantly higher urine pH was noted in the 24 g/kg group during period 5.

Urine Chemistry Values

Urine creatinine concentration at 12 g/kg was significantly increased at periods 4 and 5. When compared to vehicle-control, the 12 g/kg dose elicited a significant increase in urine osmolality at period 3 and urine potassium at period 4.

Renal Function Values

PEG 3350 caused significant decrease in creatinine clearance excretion rates during 12-24 hours observation period at 12 (48% of control clearance) or 24 (49% of control clearance) g/kg doses when compared to vehicle-treated control (6.06 ml/min/kg). Similarly, PEG 3350 caused significant decrease in sodium excretion rates during 12-24 hours observation period at 12 (36% of control clearance) or 24 (43% of control clearance) g/kg doses when compared to vehicle-treated control (0.0.14 mEq/min). Potassium clearance and free water clearance were significantly lower at 12 and 24 g/kg at period 2. In addition, fractional excretion of sodium was significantly elevated at period 2 at 24 g/kg. The following table shows the mean urine parameter changes.

Period	**0 g/kg**	**6 g/kg**	**12 g/kg**	**24 g/kg**
Specific Gravity				
0-3 hours	1.007	1.028*	1.057*	1.070**
3-6 hours	1.006	1.029*	1.063**	1.067**
6-12 hours	1.033	1.054	1.070**	1.078**
12-24 hours	1.055	1.064	1.082**	1.061
Urine Volume (ml)				
0-3 hours	183.3	52.7**	88.3*	106.0
6-12 hours	66.7	50.0	34.2*	38.8
12-24 hours	90.0	56.7	31.8*	40.3*
Urine pH				
0-3 hours	6.2	6.9	8.3**	6.1
12-24 hours	7.2	8.0	7.9	8.7*
Urine Creatinine (mg/dl)				
6-12 hours	101.1	130.7	187.5**	135.6
12-24 hours	133.7	168.4	239.8*	182.5
Urine Osmolality (mOsm/kg)				
3-6 hours	212	504	610*	497
Urine Potassium (mEq/l)				
6-12 hours	113.01	151.25	203.88*	147.65
Creatinine Clearance (ml/min/kg)				
0-3 hours	8.18	4.09	2.98*	1.07**
12-24 hours	6.06	4.26	2.94*	2.96*
Sodium Clearance (ml/min/kg)				
12-24 hours	0.014	0.015	0.005*	0.006*
Potassium Clearance (ml/min/kg)				
0-3 hours	0.454	0.235	0.199*	0.118**
Water Clearance (ml/min)				
0-3 hours	0.318	-0.107	-0.192*	-0.183*

*: p at 0.05
**: p at 0.01

Overall, all animals survived to study termination. Treatment-related clinical signs included emesis and diarrhea at all doses. Between 6- and 24-hours post-dosing, animals treated with 12 or 24 g/kg of MiraLax™ PEG-3350 elicited significant effects on urine volume, specific gravity, urine potassium and creatinine concentrations, urine osmolality and creatinine and sodium clearance rates. Significant decreases in the creatinine clearance (glomerular filtration rate) and sodium excretion rates were also observed at period 5 (12-24 hours) following treatment at 12 or 24 g/kg doses when compared to vehicle treated animals.

2.6.2.5 Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were conducted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None included.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

A pharmacokinetic and absorption/elimination study with Miralax PEG 3350 was conducted in rats at a single oral (gavage) dose of 6 g/kg using radiolabeled ^{14}C-PEG 3350. PEG 3350 was poorly (0.1-0.2% of the administered dose) absorbed and primarily excreted in the feces (60-70%). Low amount of radioactivity was found in the bile (0.16% of the dose). Mean urinary elimination ranged from approximately 10-20% of dose. The terminal half-life was about 30 hours.

In another mass balance and pharmacokinetic study in SD rats at single oral dose of 6 g/kg of ^{14}C-PEG 3350, about 89-95% of radioactive dose was excreted. The Tmax was 0.5 to 1.0 hour and $t_{1/2}$ was 13.4-15.3 hours. The main route of excretion was via feces and most of the elimination was occurred over the first 24 hours after treatment. Over the 72-hour period, about 80 and 74% of the administered dose were excreted via feces in males and females, respectively. A smaller amount (7-10%) of radioactivity was excreted in the urine over 72 hours.

Overall, results from pharmacokinetic studies using ^{14}C-PEG 3350 indicated that PEG 3350 was poorly absorbed following oral administration, primarily excreted in the feces, and if absorbed, eliminated in the urine.

2.6.4.2 Methods of Analysis

Methods of analyses were described under individual study reviews.

2.6.4.3 Absorption

Oral (Gavage) Pharmacokinetic and Absorption/Elimination Study with PEG 3350 in Rats (— 382008)

Methods: This study examined the pharmacokinetics and mass balance of PEG 3350 in rats (n = 3/sex/time point) following oral (gavage) administration at 6 g/kg (10 ml/kg) using radiolabeled PEG 3350 (^{14}C-PEG 3350, specific activity = 8.8 μCi/mg). For the pharmacokinetic group (Group 1), animals were sacrificed at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post-dose for blood collection. All plasma samples were analyzed for radioactivity using radio-HPLC (high pressure liquid chromatography). For absorption/elimination group (Group 2, 3 and 4), four animals per sex were used. For Group 2, each animal had a bile duct cannula and urine and bile were collected over the following intervals: 0-6, 6-12 and 12-24 hours post-dose and then daily through 72 hours post-dose. Feces were collected over the following intervals: 0-12 and 12-24 hours post-dose, then daily through 72 hours post-dose. For Group 3, urine and feces were collected as per Group 2 and expired carbon dioxide was collected over the following intervals: 0- 1, 1-2, 2-4, 4-6, and 6-8 hours post-dosing, then every 4 hours until 32 hours post-dosing, and then every 8 hours until 72 hours post-dosing. For Group 4, urine and feces were collected as per Group 2 and expired volatile organics were collected over the following intervals: 0-4, 4-8, and 8-12 hours post-dosing, then daily though 72 hours post-dosing. At the end of each urine collection interval, the interior surface of each cage was rinsed with deionized water and the rinse retained as a separate sample. At 72 hours post-dose, the animals were euthanized. For Group 2, a blood sample was collected as per Group 1. For Groups 3 and 4, the gastrointestinal (GI) tract was removed from each animal and the contents of the GI tract separated from the tissue. The residual carcasses from Groups 2, 3, and 4 were retained. Each cage was washed with deionized water and the wash retained. All samples were analyzed for total radioactivity using liquid scintillation techniques.

Results: Following oral administration of ^{14}C-PEG 3350 at 6 g/kg, the mean plasma Cmax was 126 pg/ml for males and 164 pg/ml for females. These concentrations represented approximately 0.1-0.2% of the administered dose. Following Tmax (2 hours), concentrations decreased in a multi-exponential manner with a terminal half-life of approximately 30 hours for both males and females. Only about 20-50% of the radioactivity in the plasma samples at Tmax eluted in the molecular weight range of PEG-3350. The concentration of PEG-3350 in the blood was less than half the concentration in the plasma. Recovery of the administered radioactivity was generally low and extremely variable. Overall mean recovery for Groups 2, 3, and 4 was 57.2, 84.5, and 63.1%, respectively. Feces were the major route of elimination for PEG-3350 in Groups 3 and 4, with 60-70% of the dose being eliminated in the feces of Group 3. Mean urinary elimination ranged from approximately 10-20% of dose. The following table shows the pharmacokinetic parameters (from page 46 of the study report).

Terminal Phase Kinetics
(Linear Regression of log Conc. vs. Time from 8–72 hr)**

Slope (b)	-0.00917	-0.01101
Y-Intercept (µg)	60.8	77.5
Coefficient of Determination (r^2)	0.953	0.976
C_{max} (µg/mL)	126	164
t_{max} (hr)	2	2
AUC_{0-24} (µg-hr/mL)	1366	1652
Elimination Rate Constant (hr^{-1})	0.0211	0.0254
Half-life (hr)	32.8	27.3

* Data were derived from Table F1 (Appendix F). N=3, except N=2 for females at 8 hr post-dosing (Animal No. 11885 excluded owing to improper dose administered), and N=1 for males at 12 hr post-dosing (Animal No. 11860 excluded because blood sample was collected at the wrong time and Animal No. 11861 excluded owing to improper dose administration).

** Linear regression only to 24 hr for females.

Absorption, Metabolism and Excretion of ^{14}C-PEG 3350 Following Oral Administration to Rats ([redacted] 7496-100)

Methods: The excretion, mass balance, and pharmacokinetics were examined in male and female SD rats after a single oral (gavage, 10 ml/kg) administration of ^{14}C-PEG 3350 (8.8 µCi/mg) at 6000 mg/kg. This study was conducted in two phases. Phase 1 (Group 1 and 2) was conducted as a preliminary study to evaluate the influence of gastrointestinal bacteria (antibiotic-treated) on the mass balance of radioactivity. At designated time points following dosing, urine, feces, and carcasses were collected. For Phase 2, rats were assigned to Groups 3 and 4. At designated time points following drug administration urine, feces, expired air, volatiles, and carcasses were collected from Group 3 animals. Blood (plasma) was collected at designated time points from animals in Group 4. The study design is shown below (from page 11 of the study report).

		Number of Animals		Dose	Target Dose Level		Target Dose Volume	Samples
Phase	Group	Male	Female	Route	(mg/kg)	(µCi/kg)	(mL/kg)	Collected
1	1	1	1	Oral	6000	100	10	Urine, Feces, Carcass
1	2[a]	1	1	Oral	6000	100	10	Urine, Feces, Carcass
2	3	4	4	Oral	6000	100	10	Urine, Feces, Expired Air, Volatiles, and Carcass
2	4	24	24	Oral	6000	100	10	Blood

a Animals were pre-treated via oral administration of antibiotics (kanamycin sulfate and lincomycin) for 5 days prior to dose administration. The antibiotic dose volume to be administered to each animal was based on body weights taken on Day 1.

Samples were analyzed for radioactivity by liquid scintillation counting (LSC). Profiles of radioactive compounds in the plasma, urine and feces were obtained by HPLC analysis and radioactive compounds were identified by liquid chromatography tandem mass spectrometry (LC/MS/MS).

Results: The results of Phase 1 indicated that the excretion of radioactivity was similar in the normal and antibiotic-treated rats (89.17% and 95.15% of radioactive dose, respectively). Concentrations of radioactivity in the plasma for Phase 2 (Group 4) were similar in males and females. There were no apparent marked gender differences in the Cmax or $AUC_{0-\infty}$ values. The excretion of radioactivity was similar in both sexes. The main route of excretion was via feces with most of the radioactivity being associated with the parent compound over the first 24 hours after dosing. Over the 72-hour Phase 2 portion of the study, about 80% and 74% of the administered dose were excreted via feces in males and females, respectively. A smaller amount of radioactivity was excreted in the urine (7-10%). A small amount (3.74%) was excreted in the expired air. The total mass balance of radioactivity was 96.7% in males and 95.8% in females.

Mean pharmacokinetic parameters are shown in the following table (from page 6 of the report).

Mean pharmacokinetic parameters for radioactivity in plasma after single oral doses of ^{14}C-PEG-3350 (6000 mg/kg) in male and female Sprague Dawley rats

Matrix	Gender	C_{max} (µg Equiv/g)[a]	T_{max} (Hours)	$AUC_{0-\infty}$ (hr·µg Equiv/g)[a]	$t_{1/2}$ (Hours)
Plasma	Male	546	1.00	7842	15.3
Plasma	Female	575	0.50	6294	13.4

a µg equivalents of ^{14}C-PEG-3350.

2.6.4.4 Distribution

None

2.6.4.5 Metabolism

None

2.6.4.6 Excretion

The sponsor submitted combined reports of absorption and excretion studies in rats, which were discussed above under section "**Absorption**".

2.6.4.7 Pharmacokinetic drug interactions

None

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

The pharmacokinetics of PEG 3350 in the plasma was studied in rats following single oral dose of 6 g/kg. The results indicated that PEG 3350 was poorly absorbed (0.1-0.2% of the administered dose), primarily excreted in the feces, and if absorbed, primarily eliminated in the urine. There was no evidence of metabolism of PEG 3350 in the rat.

2.6.4.10 Tables and figures to include comparative TK summary

The following tables (from page 29-32 of Vol. 2.1 of sponsor's submission) show comparative PK data following PEG 3350 oral administration to mice, rats, dogs and humans.

Table 2.6.4.10.1: Comparative Pharmacokinetic Data and Systemic Exposure to PEG 3350 Following Oral Administration to Mice, Rats, Dogs, and Patients

Species (route/formulation)	Dose[a] (g/kg/day)[b]	Exposure Duration	Systemic (plasma) exposure				Reference Study # (Section)	Location in Module 5	
			Males		Females				
			Cmax (ng/mL)[a]	AUC_{0-24h} (ng•h/mL)[a,c]	Cmax (ng/mL)[a]	AUC_{0-24h} (ng•h/mL)[a,c]		Mod 5. Vol. # Tab	Page
Human Adults (Oral/solution)	0.22	Single Dose	508	5619	654	7504	Braintree 851-PK-001 (2.7.2.2.2A)	4.1 5.3.3.1A Addendum #1	1-273
Human Adults (Oral/solution)	0.22	Single Dose	385	2774	945	5830	Braintree 851-PK-002 (2.7.2.2.2B)	5.1-5.2 5.3.3.1B Addendum # III	1-245 246-459
Human Adults (Oral/solution)	0.22	5 days	655	4650	914	6314			
Human Adults (Oral/solution)	0.22	7 days	611	5226	1111	8738			
Human Young Adults (Oral/solution)	0.25	7 days	353	4751	542	3947	Braintree 851-PK-005 (2.7.2.2.2D)	6.1-6.2 5.3.3.1C Addendum # 1	1-293 1-105
Human Elderly Adults (Oral/solution)	0.24	7 days	569	5309	697	6108			
ESRD Patients (Oral/solution)	0.19	7 days	Cmax = 3286.2 (males and females) AUC = 60858.4 (males and females				Braintree 851-PK-004 (2.7.2.2.2C)	7.1 5.3.3.2A Tables 5-7	1-110
Normal Volunteer Matched to ESRD Patients	0.20	7 days	Cmax = 1426.8 (males and females) AUC = 11082.4 (males and females)						

Table 2.6.4.10.1 (Continued) : Comparative Pharmacokinetic Data and Systemic Exposure to PEG 3350 Following Oral Administration to Mice, Rats, Dogs, and Patients

			Systemic (plasma) exposure					Location in Module 4	
			Males		Females				
Species (route/formulation)	Dose† (g/kg/day)	Exposure Duration	Cmax (ng/mL)*	AUC_{0-24h} (ng*h/mL)#,*	Cmax (ng/mL)*	AUC0-24h (ng*h/mL)#,*	Reference Study # (Section)	Mod. 4 Vol. # Tab	Page
Mouse Oral(gavage)/solution	1.5	Day 0	113 (0.21)	169 (0.03)	0	0	[redacted] 382011 (2.6.4.3.1)	5.1-5.3 4.2.3.2B Appendix 1 Tables 1-4	1-863
	3	Day 0	238 (0.43)	357 (0.07)	292 (0.36)	2446 (0.39)			
	6	Day 0	474 (0.87)	4271 (0.86)	978 (1.2)	3304 (0.53)			
Mouse Oral(gavage)/solution	1.5	86 days	0	0	0	0	[redacted] 382011 (2.6.4.3.1)	5.1-5.3 4.2.3.2B Appendix 1 Tables 1-4	1-863
	3	86 days	324 (0.59)	666 (0.13)	398 (0.49)	3669 (0.58)			
	6	86 days	524 (0.96)	2264 (0.45)	514 (0.63)	1383 (0.22)			
Rabbit Oral (gavage)/solution	0.5	14 days	ND	ND	317 (0.39)	624 (0.10)	[redacted] 382014 (2.6.4.3.3)	16.1-16.2 4.2.3.5.2C Appendix G Tables 1-4	1-608
	1	14 days	ND	ND	852 (1.0)	2013 (0.32)			
	2	14 days	ND	ND	1387 (1.70)	12042 (1.9)			

Data presented are for males and females after oral administration of the test article for the durations shown.
† - calculated from the mean daily dose administered in each study.
*- Numbers in parentheses represent ratios of exposure in animals to those in humans. The mean C_{max} and AUC_{0-24h} for the first 6 human studies on Table 2.6.4.10.1 were used for males (547 ng/mL and 4984 ng*h/mL) and females (816 ng/ml. and 6276 ng*h/mL)
- AUC_{0-24} in the mouse, rabbit, rat and dog. AUC_{0-last} for human studies, which is also AUC_{0-24} since the dosing interval was one day.

Table 2.6.4.10.1 (Continued): Comparative Pharmacokinetic Data and Systemic Exposure to PEG 3350 Following Oral Administration to Mice, Rats, Dogs, and Patients

			Systemic (plasma) exposure					Location in Module 4	
			Males		Females				
Species (route/formulation)	Dose† (g/kg/day)	Exposure Duration	Cmax (ng/mL)*	AUC_{0-24h} (ng*h/mL)#,*	Cmax (ng/mL)*	AUC_{0-24h} (ng*h/mL)#,*	Reference Study # (Section)	Mod 4 Vol. # Tab	Page
Rat Oral(gavage)/solution	0.5	11 days	Males were not included in this Segment II study		490 (0.6)	794 (0.13)	[redacted] 382013 (2.6.6.6.2.1)	14.1-14.2 4.2.3.5.2A Appendix F	1-455
	1.0	11 days			2084 (2.5)	4766 (0.76)			
	2.0	11 days			4546 (5.6)	12277 (1.96)			
Rat Oral(gavage)/solution	1.5	184 days	8582 (15.7)	26893 (5.4)	8912 (10.9)	24595 (3.9)	[redacted] 382009 (2.6.4.3.2)	2.1 to 7.6 4.2.3.2D Appendix 1 Tables 1-4	1-1261
	3.0	184 days	9623 (17.6)	47330 (9.5)	22308 (27.3)	59882 (9.5)			
	6.0	184 days	29269 (53.5)	186762 (37.5)	44823 (54.9)	173236 (27.6)			

ND= Not Done
Data presented are for males and females after oral administration of the test article for the durations shown.
† - calculated from the mean daily dose administered in each study.
*- Numbers in parentheses represent ratios of exposure in animals to those in humans. The mean C_{max} and AUC_{0-24h} for the first 6 human studies on Table 2.6.4.10.1 were used for males (547 ng/mL and 4984 ng*h/mL) and females (816 ng/mL and 6276 ng*h/mL)
- AUC_{0-24} in the mouse, rabbit, rat and dog. AUC_{0-last} for human studies, which is also AUC_{0-24} since the dosing interval was one day.

Table 2.6.4.10.1 (Continued): Comparative Pharmacokinetic Data and Systemic Exposure to PEG 3350 Following Oral Administration to Mice, Rats, Dogs, and Patients

Species (route/formulation)	Dose† (g/kg/day)	Exposure Duration (days)	Systemic (plasma) exposure: Males Cmax (ng/mL)*	Males AUC_{0-24h} (ng*h/mL)#,*	Females Cmax (ng/mL)	Females AUC_{0-24h} (ng*h/mL)#,*	Reference Study # (Section)	Location in Module 4: Mod 4 Vol. # Tab	Location in Module 4: Page
Dogs Oral(gavage)/solution	0.75	Day 0	1353 (2.5)	14797 (3.0)	796 (0.97)	11266 (1.8)	[redacted]	9.1 to 9.4	1-1518
	1.5	Day 0	1703 (3.1)	21024 (4.2)	4766 (5.8)	39542 (6.3)	382012		
	3	Day 0	4830 (8.8)	41496 (8.3)	8626 (10.6)	50312 (8.0)	(2.6.4.3.4)	4.2.3.2F Appendix 1 Tables 1-4	
Dogs Oral(gavage)/solution	0.75	133	2706 (4.9)	21530 (4.3)	1702 (2.1)	15543 (2.5)			
	1.5	133	2166 (4.0)	18089 (3.6)	2525 (3.1)	21181 (3.4)			
	3	133	3704 (6.8)	31775 (6.4)	5228 (6.4)	48623 (7.7)			
Dogs Oral(gavage)/solution	0.75	266	2320 (4.2)	11578 (2.3)	2187 (2.7)	15123 (2.4)			
	1.5	266	3832 (7.0)	17754 (3.6)	4738 (5.8)	30934 (4.9)			
	3	266	6170 (11.3)	28756 (5.8)	5096 (6.2)	34396 (5.5)			

Data presented are for males and females after oral administration of the test article for the durations shown.
† - calculated from the mean daily dose administered in each study.
*- Numbers in parentheses represent ratios of exposure in animals to those in humans. The mean C_{max} and AUC_{0-24h} for the first 6 human studies on Table 2.6.4.10.1 were used for males (547 ng/mL and 4984 ng*h/mL) and females (816 ng/mL and 6276 ng*h/mL)
- AUC_{0-24} in the mouse, rabbit, rat and dog. $AUC_{0-\infty}$ for human studies, which is also AUC_{0-24} since the dosing interval was one day.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Pivotal pharmacokinetic (PK) studies were tabulated under section: "**Studies reviewed within this submission**".

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The systemic toxicity of Miralax PEG 3350 was adequately evaluated in complete range of acute, subacute/subchronic and chronic toxicity studies in mice, rats and dogs. Chronic oral toxicity studies were conducted in rodent (rats up to 6 g/kg/day) up to 6 months duration and in non-rodent (dog) up to nine months (up to 3 g/kg/day) duration. The potential genotoxicity of PEG 3350 was examined in an adequate battery of genotoxicity tests. The carcinogenic potential of PEG 3350 has also been examined in CD-1 mice and (104-week) and Sprague Dawley rats (104-week). In addition, PEG 3350 has been evaluated for fertility and reproductive performance (Segment I) in rats, teratology (Segment II) in rats and rabbits and peri- and post-natal development (Segment III) in rats. Adequate safety pharmacology studies were also conducted with PEG 3350.

General toxicology: Generally, chronic toxicity studies were conducted at maximum feasible dose (MFD) levels in rats (up to 6 g/kg/day) and dogs (up to 3 g/kg/day). The recommended daily dose for the treatment of constipation is 17 grams in 240 ml of water. The highest doses in mice, rats and dogs represented 17.6-, 24.7- and 8.8- times, respectively, the recommended human dose based on body weight. In males, the AUC ratios (animal/human) for mice (6 g/kg/day), rats (6 g/kg/day) and dogs (3 g/kg/day) were 0.45, 37.5 and 5.7, respectively (the $AUC_{0\text{-}tau}$ for human was 4984 ng.hr/ml). In females, the AUC ratios (animal/human) for mice, rats and humans were 0.22, 27.6 and 6.2, respectively (the $AUC_{0\text{-}tau}$ for human was 6276 ng.hr/ml).

The target organs of toxicity appeared to vary across species. The major target organ of toxicity in the rat appeared to be the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in males at 6 g/kg/day). In dogs following oral administration of PEG 3350 for 28-days, the target organs of toxicity appeared to be the lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes; foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates), gastrointestinal tract (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue in females at 3, 6 and 9.3 g/kg/day), testes (hypospermia in the epididymides and seminiferous tubule degeneration or multiucleated spermatids of the testes) and salivary gland (atrophy). Following 9-month oral administration of PEG 3350 in dogs (up to 3 g/kg/day), the target organs of toxicity appeared to be testes (retarded development) and prostate (lymphocyte infiltrate) in the males and mammary gland (glandular hyperplasia), liver (vacuolation) and gallbladder (lymphocyte infiltrate and epithelial hyperplasia) in females.

Genetic toxicology: Miralax PEG 3350 was negative in the Ames test and did not show any clastogenic potential in the chromosome aberration test with human peripheral blood lymphocytes. It was also negative in *in vivo* oral rat micronucleus test.

Carcinogenicity: Miralax PEG 3350 has been tested in mice and rats (104-Week) following oral administration for its potential to cause carcinogenicity. Miralax PEG 3350 did not appear to show tumorigenicity in either mice or rats at the tested doses.

Reproductive toxicology: Reproduction studies have been performed in pregnant rats at oral doses up to 2 g/kg/day (about 0.95 times the recommended human oral dose based on the body surface area) and in pregnant rabbits at oral doses up to 2 g/kg/day (about 1.9 times the recommended human oral dose based on the body surface area) and have revealed no adverse effects on fertility or harm to the fetus due to Miralax PEG 3350. In pre- and post-natal developmental study in rats up to 2 g/kg/day dose (0.95 times the recommended human oral dose based on the body surface area), Miralax PEG 3350 did not show any adverse effect on F1 postnatal survival, body weight, developmental landmarks, startle response, motor activity, learning and memory and reproductive

performance, intrauterine growth and survival of F2 fetuses and external and developmental parameters of F2 fetuses.

Special toxicology: None

2.6.6.2 Single-dose toxicity

Acute oral toxicity study in female rats

Report No.	Testing Laboratory	Species/ Route	Date Started	Date Completed	Batch No.
[redacted] -382017	[redacted]	Rats/Oral (gavage)	1/8/2003	5/19/2004	1275

GLP Compliance: Statements of compliance with GLP regulations and the quality assurance unit were included in the study report.

Methods: In a previous pharmacokinetic study ([redacted] -382008) with ^{14}C-PEG-3350 in bileduct cannulated rats at 6 g/kg, four of four females and one of four males were died within 72 hours of treatment. Since other studies with PEG3350 did not show increased mortality in nay species at this dose level, the possibility was considered that bile duct cannulation or the 14C-PEG3350 was responsible for the observed mortality. Therefore, the present study was conducted to evaluate the potential toxicity of PEG 3350 and ^{14}C-PEG 3350 (8.8 μCi/mg) in bile duct-cannulated female rats (n = 5/dose) following a single oral (gavage) dosage of 6 g/kg. Initially five groups (Groups 1-5) of female Sprague-Dawley rats were used in this study. Each group consisted of five animals. Each animal received a single oral dose of PEG 3350 in the vehicle, deionized water, at a dosage level of 6 g/kg or a single oral dose of the vehicle. The dosage volume for all animals was 10 ml/kg. The study design for the non-radioactive dose is shown in the table below (from page 10 of the study report).

Designation of Initial Dose Groups (Non-Radioactive Dose)

Group Number	Treatment	Type of Animal*	Dosage Level (g/kg)	Dose Concentration (g/mL)	Dosage Volume (mL/kg)
1	Vehicle	BDC	0	0	10
2	Vehicle	BDC/BC	0	0	10
3	PEG-3350	Non-BDC	6.0	0.6	10
4	PEG-3350	BDC	6.0	0.6	10
5	PEG-3350	BDC/BC	6.0	0.6	10

*BDC=bile duct cannulated. BC=bile continuously collected beginning on the day prior to dosing. For BDC animals without collection, the cannulae remained closed.

All animals were observed for clinical signs of toxicity twice daily through 96 hours post-dosing at which time the animals in Groups 2 and 5 (those from which bile was collected) were euthanized. The animals from Groups 1, 3, and 4 were then used for additional dose groups designated as Groups 6-8. Each group consisted of five animals and each animal received a single oral dose of ^{14}C-PEG 3350 at 6 g/kg (10 ml/kg). The study design for the bile duct cannulated rats is shown below (from page 11 of the study report).

Designation of Dose Groups for the Radioactive Dose

Group Number	Treatment	Type of Animal*	Dosage Level (g/kg)	Dose Concentration (g/mL)	Dosage Volume (mL/kg)
6	^{14}C-PEG-3350	BDC/BC	6.0	0.6	10
7	^{14}C-PEG-3350	Non-BDC	6.0	0.6	10
8	^{14}C-PEG-3350	BDC	6.0	0.6	10

*BDC=bile duct cannulated. BC=bile continuously collected beginning on the day prior to dosing. For BDC animals without collection, the cannulae remained closed.

All animals were observed for signs of toxicity twice daily through 72 hours post-radiolabeled dose, at which time the animals were euthanized.

Results:

Acute Toxicity Studies with PEG 3350 in Rats

Species	Route	Dose (g/kg)	Maximum Nonlethal Dose (g/kg)		Minimum Lethal Dose (g/kg)		Time to death
			Male	Female	Male	Female	
Rats	Oral	6	-	6.0	-	-	-

In an acute oral toxicity study in rats, animals were treated with PEG 3350 at 6 g/kg. No significant clinical observations were noted in either non bile-duct-cannulated or bile duct-cannulated animals. Two out of ten animals that received unlabeled PEG 3350 and from which bile was continuously collected were found in a moribund condition. However, one out of five animals that received the vehicle and from which bile was continuously collected was found dead, indicating that the moribund condition of the treated animals was probably related to bile duct cannulation and were not test article related. In this study, only one dose was tested. Therefore, the minimum nonlethal dose could not be determined. In addition, the animals were observed for 72 hours only instead of 2 weeks for a conventional acute toxicity study.

2.6.6.3 Repeat-dose toxicity

Study title: 3-Month Oral (Gavage) Toxicity Study with PEG 3350 in CD-1 Mice

Key study findings: In a 3-month oral gavage study in CD-1 mice, animals were tested at 0 (water), 1.5, 3 and 6 g/kg/day. The target organ of toxicity could be the gastrointestinal tract (small intestine: minimal to mild attenuation of the mucosal epithelium characterized by shortened/fused villi and without crypt gland degeneration; large intestine: minimal to mild attenuation of the mucosal epithelium and luminal distention) in both sexes based on the dose-related increase in incidences of these findings. However, these changes were also observed in some control animals. The NOAEL could not be determined, as treatment-related changes in the gastrointestinal tract were observed at all tested doses in both sexes.

Study no.: [redacted]-382011
Volume #, and page #: 5.1, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: July 29, 2002
GLP compliance: A statement of compliance was included.
QA report: yes (X) no ( )
Drug, lot #, and % purity: PEG 3350, Lot. No. 1275, [redacted]

Methods:

Doses: 1.5, 3 and 6 g/kg/day. Dose selection was based on the results of a 14-day oral (gavage) dose ranging study in mice ([redacted] 382010) at 1.5, 3, 5 and 6 g/kg/day (10 ml/kg). In the dose ranging study, there was no mortality or treatment-related clinical signs or histopathologic findings. Based on the results of this dose ranging study, the highest dose for the current study was selected as 6 g/kg/day.

Species/strain: Mice/CD-1

Number/sex/group or time point (main study): 20/sex/group

Route, formulation, and volume: Oral, solution, 10 ml/kg

Satellite groups used for toxicokinetics: 38/sex/group. The study design is shown below (from page 17 of the study report).

Toxicology Groups [redacted] -382011)

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals	
					Males	Females
1	Vehicle	0	0	10	20	20
2	MiraLax® PEG-3350	1.5	0.15	10	20	20
3	MiraLax® PEG-3350	3	0.3	10	20	20
4	MiraLax® PEG-3350	6	0.6	10	20	20

Toxicokinetic Groups [redacted] -382011A)

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals	
					Males	Females
2A/1[a]	MiraLax® PEG-3350	1.5	0.15	10	38	38
3A/2[a]	MiraLax® PEG-3350	3	0.3	10	38	38
4A/3[a]	MiraLax® PEG-3350	6	0.6	10	38	38

[a] = Computer protocol designation

Age: 38 days

Weight: 21.3-23.6 g

Observations and Times:

Mortality: Animals were observed twice daily for mortality.

Clinical signs: Animals were observed twice daily for clinical signs.

Body weights: Body weights were recorded on a weekly basis.

Food consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopy was conducted on Week -1 and 13.

Hematology: Hematology was conducted at necropsy.

Clinical chemistry: Clinical chemistry was conducted at necropsy.

Gross pathology: Gross pathological examination was performed at necropsy.

Organ weights: The following organs were weighed from all animals: adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries and oviducts, spleen, testes, thyroid and parathyroids and uterus.

Histopathology: The following organs/tissues (from page 25 of the study report) were examined for histopathology from all animals in the control and high dose groups and all animals found dead.

Adrenal glands (2)
Aorta
Bone with marrow
  Femur with knee joint
  Sternum
Bone marrow smear
  (from femur)[a]
Brain
  Crebrum (2 levels)
  Cerebellum with pons/medulla
Exorbital lacrimal glands (2)
Epididymides (2)[b]
Eyes with optic nerve (2)[c]
Gallbladder
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Harderian glands (2)
Heart
Kidneys (2)
Liver
Lungs (including bronchi, fixed by
  inflation with fixative)
Lymph node
  Mesenteric
Mammary gland (female only)
Ovaries with oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands
  [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin
Spinal cord
  Cervical
  Midthoracic
  Lumbar
Spleen
Testes (2)[b]
Thymus
Thyroid [with parathyroids (2)][d]
Trachea
Urinary bladder
Uterus with vagina
Zymbals glands (2)
All gross lesions

Toxicokinetics: Blood samples were collected on study days 0 and 86 at 0, 1, 2, 4, 8 and 24 hours post-dose.

Results:

Mortality: There were no treatment-related mortalities. One female at 1.5 g/kg/day was found dead on study day 4. The sponsor stated that this death was not considered test article-related, although the cause of death could not be determined. In addition, four males and one female at 3 g/kg/day were found dead on study days 56 or 57. All of these deaths were attributed to gavage error.

Clinical signs: Treatment-related clinical signs (soft feces) were observed in a dose-related manner at 1.5, 3 and 6 g/kg/day. The incidences of soft feces were 0 of 0, 0 of 0, 2 of 2 and 7 of 6 animals at the control, 1.5. 3 and 6 g/kg/day group males, respectively,

and 0 of 0, 3 of 3, 9 of 7 and 37 of 17 animals at the control, 1.5, 3 and 6 g/kg/day group females, respectively.

Body weights: The mean initial and final weights of control males were 23.6 and 35.6 g, respectively. The mean initial and final body weights of control females were 21.3 and 29.8 g, respectively. There were no significant treatment-related changes.

Food consumption: The mean initial and final food consumption in control males were 5.6 and 4.5 g/animal/day, respectively. The mean initial and final food consumption in control females were 5.7 and 6.0 g/animal/day, respectively. There were no significant treatment-related effects.

Ophthalmoscopy: There were no test article-related ophthalmic findings at any dose level.

Hematology: There were no treatment-related effects on hematology parameters.

Clinical chemistry: There were no treatment-related effects on serum chemistry parameters.

Gross pathology: No significant treatment-related changes were observed.

Organ weights: There were no treatment-related effects on organ weights.

Histopathology: Treatment-related changes were observed in the gastrointestinal tract (small intestine: minimal to mild attenuation of the mucosal epithelium characterized by shortened/fused villi and without crypt gland degeneration; large intestine: minimal to mild attenuation of the mucosal epithelium and luminal distention) in both sexes. In the stomach, chronic inflammation and mucosal glandular hyperplasia were noted and were not considered to be treatment-related as they were also seen in the controls. In addition, lymphoid hyperplasia was seen in all groups, including the controls. The incidence or severity of lymphoid hyperplasia was not considered to be treatment-related. One male, (No. 6010) at 1.5 g/kg/day group had focal and segmental intestinal amyloidosis (lamina propria with eosinophilic acellular deposit). This change was considered spontaneous and incidental. The following table (from page 616 of the study report) shows the incidences of gastrointestinal findings.

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A 3-Month Oral (Gavage) Toxicity Study of Miralax® PEG 3350 in Mice
[redacted]-382011

Table 3: Incidence of gastrointestinal findings by tissue, group and sex[a]

Group	1		2		3		4	
Tissue/Diagnosis	M	F	M	F	M	F	M	F
CECUM								
Mucosal epithelial attenuation	0	0	0	0	0	0	1/20* (5%)	0
Luminal dilatation	0	0	2/20 (10%)	0	1/16 (6%)	0	2/20 (10%)	0
COLON								
Mucosal epithelial attenuation	0	0	1/20 (5%)	0	0	1/19 (5%)	1/20 (5%)	2/20 (10%)
Luminal dilatation	1/20 (5%)	0	2/20 (10%)	1/19 (5%)	0	1/19 (5%)	6/20 (30%)	3/20 (15%)
DUODENUM								
Mucosal epithelial attenuation	0	0	0	0	0	0	3/20 (15%)	0
Luminal dilatation	0	0	0	0	0	0	0	0
ILEUM								
Mucosal epithelial attenuation	2/20 (10%)	1/20 (5%)	2/20 (10%)	0	1/16 (6%)	1/19 (5%)	7/20 (35%)	5/20 (25%)
Luminal dilatation	0	0	1/20 (5%)	0	0	1/19 (5%)	0	1/20 (5%)
JEJUNUM								
Mucosal epithelial attenuation	3/20 (15%)	3/20 (15%)	1/20 (5%)	0	0	2/19 (11%)	12/20 (60%)	7/20 (35%)
Luminal dilatation	0	0	1/20 (5%)	0	0	2/19 (11%)	0	4/20 (20%)
Inflammation, chronic, serosal	1/20 (5%)	0	0	0	0	0	0	0
RECTUM								
Mucosal epithelial attenuation	0	0	2/20 (10%)	1/19 (5%)	2/16 (13%)	1/19 (5%)	0	1/20 (5%)
Luminal dilatation	0	0	1/20 (5%)	0	3/16 (19%)	1/19 (5%)	3/20 (15%)	2/20 (10%)
STOMACH								
Inflammation, chronic	1/20 (5%)	2/20 (10%)	3/20 (15%)	1/19 (5%)	1/16 (6%)	0	0	0
Mucosal hyperplasia, glandular	5/20 (25%)	9/20 (45%)	5/20 (25%)	3/19 (16%)	4/16 (25%)	1/19 (5%)	7/20 (35%)	5/20 (25%)

[a] Only animals surviving to the end of the experiment are included. * The number in the numerator is the number of observations and in the denominator is the number of tissues per group. The percent was calculated by dividing the numerator by the denominator and multiplying by 100.

Group 1: Control
Group 2: 1.5 g/kg/day
Group 3: 3.0 g/kg/day
Group 4: 6.0 g/kg/day

Toxicokinetics: Exposures to PEG 3350 generally increased in a dose proportional manner over the dose range of 1.5 to 6 g/kg/day. There appeared to be gender differences

in $AUC_{0\text{-}24h}$ and Cmax values, with male mice having higher $AUC_{0\text{-}24h}$ and Cmax values than female mice following dosing at 1.5 g/kg/day on Day 0 and female mice had higher $AUC_{0\text{-}24h}$ values than male mice following dosing at 3 g/kg/day on Days 0 and 86. The TK parameters are summarized in the following table (from page 35 of the study report).

TOXICOKINETIC RESULTS

Gender/ PEG-3350 (g/kg/day)	PEG-3350 Results $AUC_{0\text{-}24h}$ (ng•h/mL)		C_{max} (ng/mL)		t_{max} (h)	
	Day 0	Day 86	Day 0	Day 86	Day 0	Day 86
Males						
1.5	169	0	113	0	2	N/A
3	357	666	238	324	2	2
6	4271	2264	474	524	1	2
Females						
1.5	0	0	0	0	N/A	N/A
3	2446	3669	292	398	1	2
6	3304	1383	978	514	1	2

N/A = Not applicable; t_{max} could not be determined owing to no measurable concentration of PEG-3350 at any time point.

Summary: In a 3-month oral gavage study in CD-1 mice, animals were tested at 0 (water), 1.5, 3 and 6 g/kg/day. The target organ of toxicity appeared to be the gastrointestinal tract (small intestine: minimal to mild attenuation of the mucosal epithelium characterized by shortened/fused villi and without crypt gland degeneration; large intestine: minimal to mild attenuation of the mucosal epithelium and luminal distention) in both sexes based on the dose-related increase in incidences of these findings. However, these changes were also observed in some control animals. The NOAEL could not be determined, as treatment-related changes in the gastrointestinal tract were observed at all tested doses in both sexes.

Study title: 90-Day Oral (Gavage) Toxicity Study with Carbowax®PEG 3350 in Rats

Key study findings: In a 90-day oral gavage study in Sprague Dawley rats, animals were tested with Carbowax PEG 3350 at 1.5, 3.0 and 6.0 g/kg/day. The target organs of toxicity could not be identified in the absence of any significant treatment-related histopathological findings. The NOAEL appeared to be 6 g/kg/day.

Study no.: — 95027
Volume #, and page #: 6.1, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: January 5, 2000
GLP compliance: A statement of compliance was included.
QA report: yes (X) no ( )

Drug, lot #, and % purity: Carbowax®PEG 3350, Lot No. 0000222609. Purity data was not provided.

Methods:

Doses: 1.5, 3.0 and 6.0 g/kg/day

Species/strain: Rats/Sprague-Dawley (SD)

Number/sex/group or time point (main study): 10/sex/group

Route, formulation, and volume: Oral, solution, 10 ml/kg

Satellite groups used for toxicokinetics or recovery: None

Age: 29 days

Weight: 138-166 g

Study design: None. The study design is shown below.

Group	Test Article	Dose (g/kg/day)	Conc. (g/ml)	Dose Volume (ml/kg)	Number of Animals	
					Males	Females
1	Water	0	0	10	10	10
2	PEG 3350	1.5	0.15	10	10	10
3	PEG 3350	3.0	0.3	10	10	10
4	PEG 3350	6.0	0.6	10	10	10

Observations and Times:

Mortality: Mortality was observed twice daily.

Clinical signs: Clinical signs were observed twice daily.

Body weights: Body weights were recorded on a weekly basis.

Food consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopy was conducted on Week -2 and 12.

Hematology: Hematology was conducted at necropsy.

Clinical chemistry: Clinical chemistry was conducted at necropsy.

Urinalysis: Urinalysis was conducted at necropsy.

Gross pathology: Gross pathology was performed at necropsy.

Organ weights: The following organs were weighed from all animals at necropsy: adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes with epididymides, thymus, thyroid with parathyroid and uterus.

Histopathology: The following organs/tissues (from page 21 of the study report) were examined for histopathology from all animals in the control and high dose groups and all animals found dead.

Adrenal (2)
Aorta
Bone with marrow
  Sternebrae
Bone marrow smear[a]
Brain
  Forebrain
  Midbrain
  Hindbrain
Epididymides (2)[c]
Eyes with optic nerve (2)[b]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Heart
Kidneys (2)
Lacrimal glands (including Harderian gland)
Liver (sections of two lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph node
  Mesenteric
  Submandibular
Mammary gland (females only)
Ovaries with oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands [submaxillary (2)]
Seminal vesicles (2)
Skeletal muscle (vastus medialis)
Skin
Spinal cord (cervical, midthoracic, lumbar)
Spleen
Testes (2)[c]
Thymus
Thyroid [with parathyroids if present (2)]
Trachea
Urinary bladder
Uterus with vagina
All gross lesions

[a] = Not taken from animal found dead, not placed in formalin; to be examined only if scientifically warranted.
[b] = Placed in Davidson's solution
[c] = Placed in Bouin's solution

Toxicokinetics: None

Results:

Mortality: One male (no. 37512) at 6.0 g/kg/day group was found dead on study day 62. There were no notable clinical signs prior to death and the death was considered incidental in nature and not related to test article.

Clinical signs: There were no treatment-related clinical signs at any dose level. Head tilt was noted for one female at 1.5 g/kg/day. This finding was not considered treatment-related, since it was limited to a single animal in the low dose group.

Body weights: The mean initial and final weight of control males were 166 and 555 g, respectively. The mean initial and final weight of control females were 138 and 314 g, respectively. There were no significant treatment-related changes.

Food consumption: The mean initial and final food consumption in control males were 24 and 26 g/animal/day, respectively. The mean initial and final food consumption in control females were 18 and 18 g/animal/day, respectively. No test article-related effects were noted on food consumption.

Ophthalmoscopy: No treatment-related ophthalmologic changes were seen at any dose level.

Hematology: No test article-related changes in hematology parameters were observed in any treated groups.

Clinical chemistry: Serum chemistry parameters were unaffected by treatment.

Urinalysis: No treatment-related changes were observed at any dose level.

Gross pathology: No treatment-related changes were observed.

Organ weights: Mean uterine weights (absolute: 128% of control, control = 0.55 g, relative to body weight: 127% of control, control = 0.188 and relative to brain weight: 1305 of control, control = 28.521) were higher at 1.5 g/kg/day group females. However, similar changes were not noted in the 3.0 and 6.0 g/kg/day females and these changes were not considered treatment-related. Mean adrenal gland weight (relative to brain weight: 119% of control, control = 3.343) was higher in the 6.0 g/kg/day group females.

Histopathology: There were no significant treatment-related findings at any dose level.

Summary: In a 90-day oral gavage study in SD rats, animals were tested with Carbowax PEG 3350 at 1.5, 3.0 and 6.0 g/kg/day. The target organs of toxicity could not be identified in the absence of any significant treatment-related histopathological findings. The NOAEL appeared to be 6 g/kg/day.

Study title: 6-Month Oral Toxicity Study with Miralax PEG 3350 in Rats (As Part of a 104-Week Oral Gavage Carcinogenicity Study in Rats)

Key study findings: In a 6-month oral gavage study in rats, animals were treated with PEG 3350 at 1.5, 3 and 6 g/kg/day. The NOAEL could not be determined, as treatment-related effects were seen at all dose levels. The target organ of toxicity appeared to be the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in 5 of 12 males at 6 g/kg/day).

Study no.: [redacted] 382009
Volume #, and page #: 7.1, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: July 1, 2002
GLP compliance: A statement of compliance was included.
QA report: yes (X) no ( )
Drug, lot #, and % purity: Miralax PEG 3350, Lot No. 1275, [redacted]

Methods:

Doses: 1.5, 3.0 and 6.0 g/kg/day. Dose selection for this study was based on data from the previous 3-month study in rats with PEG 3350 at 1.5, 3 and 6 g/kg/day. In that study, there were no test article-related findings at any dose level. In addition, the high dose at 6 g/kg/day, administered using the dose volume of 10 ml/kg, allowed for the maximum amount of test article for dosing as a weight to volume mixture where the formulation was considered as a solution at room temperature (solubility = 0.62 g/ml) or the maximum feasible dose (MFD).

Species/strain: Rats/Sprague Dawley

Number/sex/group or time point (main study): 15/sex/dose

Route, formulation, and volume: Oral, solution in water, 10 ml/kg

Satellite groups used for toxicokinetics: 9/sex/group

Age: 37 days

Weight: 142-157 g

Study design: This is a part of a 104-week oral carcinogenicity study in rats. The following table (from page 22 of the study report) shows the study design.

Toxicology Groups ([redacted] 382009M and 382009F)[a]

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals Males	Number of Animals Females
1	Vehicle	0	0	10	65	65
2	MiraLax™ PEG-3350	1.5	0.15	10	65	65
3	MiraLax™ PEG-3350	3	0.3	10	65	65
4	MiraLax™ PEG-3350	6	0.6	10	65	65

Toxicokinetic Groups [redacted] -382009A and 382009B)[b]

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals Males	Number of Animals Females
2A/1[c]	MiraLax™ PEG-3350	1.5	0.15	10	11	11
3A/2[c]	MiraLax™ PEG-3350	3	0.3	10	11	11
4A/3[c]	MiraLax™ PEG-3350	6	0.6	10	11	11

[a] = The target group sizes for the chronic toxicity evaluation were 15 animals/sex/group for Groups 1, 2, 3 and 4. Due to the number of unscheduled deaths, 12, 12, 12 and 12 males in Groups 1, 2, 3 and 4, respectively, and 15, 14, 13 and 10 females in Groups 1, 2, 3 and 4, respectively, were necropsied after six months of dosing.

[b] = Groups 2A, 3A and 4A were dosed with the test article formulations in the same fashion as for Groups 2, 3 and 4, respectively. The target group sizes were nine animals/sex. Two additional rats/sex/group were added to accommodate the potential for dosing/bleeding accidents.

[c] = Computer protocol designation.

Observations and Times:

Mortality: Mortality was observed twice daily.

Clinical signs: Clinical signs were observed twice daily.

Body weights: Body weights were recorded weekly on Week -1 to 14 and then biweekly.

Food consumption: Food consumption was recorded weekly on Week -1 to 14 and then biweekly.

Ophthalmoscopy: Ophthalmoscopy was conducted on Week -1 and 25.

Hematology: Hematology was conducted at necropsy.

Clinical chemistry: Clinical chemistry was performed at necropsy.

Urinalysis: Urinalysis was conducted at necropsy.

Gross pathology: Gross pathology was conducted at necropsy.

Organ weights: The following organs were weighed from all animals at necropsy: adrenals, brain, epididymides, heart, kidneys, liver, ovaries and oviducts, prostate, spleen, testes, thyroid with parathyroid and uterus.

Histopathology: The following organs/tissues as shown in the following table (from page 33 of the study report) were examined histopathologically from all control and high dose animals.

Adrenals (2)
Aorta
Bone with marrow
  Femur
  Sternum
Bone marrow smear[a]
Brain
  Cerebrum level 1
  Cerebrum level 2
  Cerebellum with medulla/pons
Clitoral glands (2)
Epididymides (2)[b]
Eyes with optic nerve (2)[c]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Harderian glands (2)
Heart
Kidneys (2)
Lacrimal glands
  Exorbital (2)
Liver (sections of two lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph nodes
  Mandibular (2)
  Mesenteric
Mammary gland (females only)
Nasal turbinates[e]
Ovaries with oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin (inguinal)
Spinal cord (cervical, mid-thoracic, lumbar)
Spleen
Testes (2)[b]
Thymus (if present)
Thyroid [both lobes with parathyroids (2)][d]
Tongue
Trachea
Urinary bladder (inflated with fixative)
Uterus with cervix
Vagina
Zymbal's gland
All gross lesions (including masses)

Toxicokinetics: Blood samples were collected from TK animals (3/sex/dose) on study day 184 at 0, 1, 2, 6, 12 and 24 hours post-dose.

Results:

Mortality: Two males each in the control, 1.5, 3 and 6 g/kg/day groups and one female each in the 1.5, 3 and 6 g/kg/day groups, respectively, were found dead during study days 14 to 159. One male each in the 1.5 and 3 g/kg/day groups were euthanized *in extremis* on study days 52 and 99, respectively. One male each in the control and 6 g/kg/day group and one and four females in the 3 and 6 g/kg/day groups, respectively, were considered accidental deaths during study days 12 to 80. The cause of death for nine of the males and three of the females was not determined, two males and five females died from apparent gavage errors (accidental deaths) and one male died from malignant lymphoma. None of these deaths were considered related to the treatment in the absence of any correlating microscopic findings. The following table shows the mortality in males and females.

Week	0 g/kg/day		1.5 g/kg/day		3.0 g/kg/day		6.0 g/kg/day	
	M	F	M	F	M	F	M	F
0								
1							1 (AD)	
2								1 (FD) 1 (AD)
3						1 (FD)		3 (AD)
4								
5								
6	1 (FD)		1 (FD)					
7			1 (EE)					
8								
9					1 (FD)			
10	1 (AD)							
11						1 (AD)		
12								
13			1 (FD)					
14					1 (EE)		1 (FD)	
15	1 (FD)							
16								
17							1 (FD)	
18					1 (FD)			
19								
22				1 (FD)				
TOTAL	3	0	3	1	3	2	3	5

M = Male
F = Female
AD = Accidental death
FD = Found dead
EE = Euthanized in extremis

Clinical signs: Clinical observations noted 24-hours prior to death for animals that were euthanized *in extremis* included hypoactivity, rales, gasping, emaciation, dermal atonia, paleness of the body, yellow and/or red material on various body surfaces (eyes, mouth, nose, ventral trunk, forelimbs, hindlimbs, urogenital area and/or anogenital area) and decreased defecation. Animals that were found dead did not have any clinical observations noted 24-hours prior to death. Test article-related findings of soft feces and brown material on the anogenital area were noted at 6 g/kg/day group. These findings were more prevalent in the males. The incidences (total occurrence/number of animals) of soft feces at the weekly detailed physical examinations and at the time of dosing were 41/23 and 107/33, respectively, for the 6 g/kg/day group males, compared to 1/1 and 16/11 at these same two time points, respectively, for the control group males. The incidences of soft feces at the weekly detailed physical examinations and at the time of dosing were 3/3 and 9/5, respectively, for the 6 g/kg/day group females, compared to 0/0 and 2/2 at these same two time points, respectively, for the control group females.

Body weights: The mean initial and final weights of the control males were 157 and 592 g, respectively. The mean initial and final weights of control females were 142 and 331 g, respectively. There were no significant treatment-related changes.

Food consumption: The mean initial and final food consumption in control males was 22 and 25 g/animal/day, respectively. The mean initial and final food consumption control females were 17 and 19 g/animal/day, respectively. There were no significant test article-related effects on food consumption.

Ophthalmoscopy: No ocular findings indicative of a test article-related effect were observed at any dose level.

Hematology: There were no significant treatment-related changes.

Clinical chemistry: Treatment-related increase in mean serum calcium (11.9 and 12.2 mg/dl, for males and females, respectively, mean control ranges = 9.8-12.0 mg/dl), phosphorus (8.5, 9.0 and 8.4 mg/dl in the 3 and 6 g/kg/day group males and 6 g/kg/day group in females, control = 4.0-8.0 mg/dl), anion gap (the anion gap is the difference between the summed values of the measured cations and the summed values of the measured anions) levels and decreased bicarbonate levels were noted in the 3 and/or 6 (24 and 21 mEq/l in males and females, respectively; control = Approximately 26 mEq/l) g/kg/day group males and females, indicating acidosis. In addition, a significant decrease (87% of control) in serum urea nitrogen was noted in the 3 g/kg/day (13.1 mg/dl, control = 15.1 mg/dl) group females when compared to the control group. In the absence of a dose-response relationship or similar changes in the males, this finding was considered incidental and of no biological significance. Overall, the hypercalcemia, hyperphosphataemia and hypobicarbonatemia, and the subsequent mild acidosis, were mostly considered to be due to water and electrolyte loss from the gastrointestinal tract.

Urinalysis: Test article-related alterations in urine chemistry included increased mean specific gravity (1.056, control = 1.033) and lower mean total urine volume (5.7 ml vs.

8.2 ml in control) in the 6 g/kg/day group males and decreased mean urine pH values in the 6 g/kg/day group males (6.4 vs. 7.3 in control) and females (6.1 vs. 6.8 in control) when compared to control. In addition, a significant increase in mean urine potassium concentration was noted in the 1.5 (146% of control, control = 147.86 mEq/l) and 6 g/kg/day (157% of control, control = 147.86) group males and an increase in mean urine creatinine concentration in the 6 g/kg/day (147% of control, control = 158.8 mg/dl) group males.

Gross pathology: There were no significant treatment-related changes.

Organ weights: No significant treatment-related changes were observed.

Histopathology: Treatment-related histopathological changes were observed in the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in 5 of 12 males at 6 g/kg/day).

Toxicokinetics: The systemic exposures (AUC_{0-24h}) to PEG 3350 in male and female rats increased in a dose-proportional manner. The Tmax ranged from 1 to 2 hours. There was no apparent gender difference in the AUC values, however, female rats tended to have higher Cmax values than male rats. The toxicokinetic (TK) parameters are shown in the following table (from page 44 of the study report).

	Males			Females		
Dose Level	AUC_{0-24} (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)
1.5 g/kg/day Day 184	26893	8582	1	24595	8912	1
3 g/kg/day Day 184	47330	9623	2	59882	22308	1
6 g/kg/day Day 184	186762	29269	2	173236	44823	2

Summary: In a 6-month oral gavage study in rats, animals were treated with PEG 3350 at 1.5, 3 and 6 g/kg/day. The NOAEL could not be determined, as treatment-related effects were seen at all dose levels. The target organ appeared to be the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in 5 of 12 males at 6 g/kg/day).

Study title: 28-Day Oral (Gavage) Toxicity Study with Miralax PEG 3350 in Dogs

Key study findings: In a 28-day oral (gavage) toxicity study in Beagle dogs, animals were treated at 3, 6 and 9.3 g/kg/day. The target organs of toxicity appeared to be lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes; foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates), gastrointestinal tract (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue in females at 3, 6 and 9.3 g/kg/day), testes (hypospermia in the epididymides and seminiferous tubule degeneration or multiucleated spermatids of the testes) and salivary gland (atrophy). The NOAEL could not be determined as treatment-related findings were seen at all dose levels.

Study no.: [redacted] 382005
Volume #, and page #: 8.1, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: April 24, 2002
GLP compliance: A statement of compliance was included.
QA report: yes (X) no ( )
Drug, lot #, and % purity: PEG 3350, Lot. No. 1275, [redacted]

Methods:

Doses: 3, 6 and 9.3 g/kg/day

Species/strain: Dogs/Beagle

Number/sex/group or time point (main study): 4/sex/dose

Route, formulation, volume: Oral, solution, 15 ml/kg

Satellite groups used for toxicokinetics or recovery: None

Age: 6 months

Weight: 8.0-9.9 kg

Study design: The study design is shown in the following table (from page 16 of the study report).

Group Number	Test Article	Dosage Level (g/kg/dose)	Concentration (g/mL)	Dose Volume (mL/kg/dose)	Number of Animals Males	Females
1	Vehicle	0	0	15	4	4
2	MiraLax® PEG-3350	3	0.2	15	4	4
3	MiraLax® PEG-3350	6	0.4	15	4	4
4	MiraLax® PEG-3350	9.3	0.62	15	4	4

Observations and Times:

Mortality: Animals were observed twice daily.

Clinical signs: Clinical signs were observed daily.

Body weights: Body weights were recorded on a weekly basis.

Food consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopy was conducted on Week -1 and 4.

Electrocardiography (ECG): Electrocardiography was conducted on Week -2 and 3.

Hematology: Hematology was performed on Week -1 and 3.

Clinical chemistry: Clinical chemistry was performed on Week -1 and 3.

Urinalysis: Urinalysis was conducted on Week -1 and 3.

Gross pathology: Gross pathology was conducted at necropsy.

Organ weights: The following organs were weighed from all animals at necropsy: adrenals, brain, epididymides, heart, kidney, liver, ovaries, pituitary, prostate, spleen, testes, thyroid and parathyroids.

Histopathology: The following (from page 26 of the study report) tissues/organs were examined from all animals.

Adrenals (cortex and medulla)(2)
Aorta
Bone with marrow
  Femur
  Sternum
Bone marrow smear[a]
Brain
  Cerebrum level 1
  Cerebrum level 2
  Cerebellum with medulla/pons
Epididymides (2)[b]
Eyes with optic nerve (2)[c]
Gallbladder
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon (descending)
  Rectum
Heart
Kidneys (2)
Liver (sections of two lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph node
  Mandibular
  Mesenteric
Mammary gland (females only)
Ovaries (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands [mandibular (2)]
Skeletal muscle (rectus femoris)
Skin
Spinal cord
  Cervical
  Midthoracic
  Lumbar
Spleen
Testes (2)[b]
Thymus
Thyroid [with parathyroids (2)][d]
Tongue
Trachea
Urinary bladder
Uterus with cervix
Vagina
Gross lesions (when possible)

Toxicokinetics: On Days 0 and 27, blood samples were collected for TK analyses from all animals at 0, 0.5, 1, 2, 4, 8, and 24 hours post-dose.

Results:

Mortality: None

Clinical signs: Test article-related clinical sings included emesis, wet clear material around the mouth and abnormal excreta (diarrhea. soft feces and/or mucoid feces) in all test article-treated groups. The following table (from page 30 of the study report) shows the summary of clinical signs.

Summary of Number of Occurrences of Selected Clinical Observations[a]								
	Males				Females			
Dose Level (g/kg/dose)	0	3	6	9.3	0	3	6	9.3
Diarrhea	0	47	67	66	8	51	75	56
Soft Feces[b]	20	38	43	53	11	41	46	72
Emesis[c]	7	22	39	69	3	9	33	37

Summary of Total % Findings of Selected Clinical Observations[a]								
	Males				Females			
Dose Level (g/kg/dose)	0	3	6	9.3	0	3	6	9.3
Diarrhea	0%	13%	19%	19%	2%	15%	22%	16%
Soft Feces[b]	6%	11%	12%	15%	3%	12%	13%	21%
Emesis[c]	2%	6%	11%	20%	1%	3%	10%	11%

[a] - Clinical observations for detailed physical examinations, prior to dosing, one hour post-dosing and three hours post-dosing combined.
[b] - Soft feces observations include findings of soft feces and mucoid feces.
[c] - Emesis observations include findings of emesis containing white, yellow and/or food material.

Body weights: The mean initial and final weights of control males were 9.9 and 11.4 kg, respectively. The mean initial and final weights of control females were 8.1 and 8.9 kg, respectively. There were no significant treatment-related changes.

Food consumption: The mean initial and final food consumption in control males were 334 and 389 g/animal/day, respectively. The mean initial and final food consumption in control females were 260 and 305 g/animal/day, respectively. Food consumption was unaffected by treatment.

Ophthalmoscopy: No treatment-related changes were observed.

ECG: There were no treatment-related electrocardiographic findings.

Hematology: No treatment-related changes were observed on hematology parameters.

Clinical chemistry: No significant test article-related effects were noted on serum chemistry parameters.

Urinalysis: There were no treatment-related changes.

Gross pathology: No test article-related macroscopic findings were noted at necropsy.

Organ weights: No significant treatment-related changes were observed.

Histopathology: Treatment-related changes were limited to the lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes). This change was seen in one of four dogs in

each of the 3, 6 and 9.3 g/kg/dose group females and in one of four dogs in each of the 6 and 9.3 g/kg/day group males. In the one male and one female in the 9.3 g/kg/day group, fibrosis extended to and thickened the pleura. Fibrosis was not observed in any control group dogs. Test article-treated dogs showed foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates. These changes were seen in one to two of four dogs at 6 and 9.3 g/kg/day, respectively.

In addition, treatment-related histopathological changes were also seen in the intestinal tracts (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue was seen in one to two of four females in each of the 3, 6 and 9.3 g/kg/day). In addition, minimal salivary gland atrophy was seen in one of four males in the 3, 6 and 9.3 g/kg/day groups, however, this was not observed in the control group or any of the female groups. In addition, hypospermia in the epididymides and seminiferous tubule degeneration or multiucleated spermatids of the testes were also seen across all groups. The histopathological changes are shown in the following table.

Tissue Finding	Males (n = 4)				Females (n = 4)			
	0 g/kg/d	3 g/kg/d	6 g/kg/d	9.3 g/kg/d	0 g/kg/d	3 g/kg/d	6 g/kg/d	9.3 g/kg/d
LUNG								
Inflammation, subacute	4	2	3	4	2	3	3	3
Fibrosis, pleural	0	0	0	1	0	0	0	1
Fibrosis, interstitial	0	0	1	1	0	1	1	1
Inflammation, granulomatous	1	0	0	0	-	-	-	-
Infiltrate, mononuclear, perivascular	0	0	2	2	0	2	0	1
Macrophage, alveolar	0	0	1	0	0	1	1	0
CECUM								
Hemorrhage	0	1	2	0	0	1	0	3
Inflammation, subacute	0	0	1	0				
Hyperplasia, lymphoid					0	2	1	2
COLON								
Abscess, crypts	0	1	0	0	1	0	1	0
Hemorrhage	0	0	0	1	0	1	1	0
ILEUM								
Hemorrhage	0	2	0	0	1	1	1	2
Inflammation, subacute	-	-	-	-	0	0	1	0
RECTUM								
Inflammation, subacute	0	0	0	1	1	3	2	0
Abscess, crypts	0	0	0	1	-	-	-	-
Hemorrhage	1	1	0	0	0	2	1	1
Hyperplasia, lymphoid	-	-	-	-	0	0	0	1
SALIVARY GLAND								
Atrophy	0	1	1	1	-	-	-	-

Infiltrate, lymphocyte	0	0	0	1	1	3	1	3
TESTES								
Spermatids, multinucleated	2	3	2	3	-	-	-	-
Degeneration, somniferous tubule	2	0	2	1	-	-	-	-

Toxicokinetics: TK data were not provided in the study report.

Summary: In a 28-day oral (gavage) toxicity study in Beagle dogs, animals were treated at 3, 6 and 9.3 g/kg/day. The target organs of toxicity appeared to be lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes; foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates), gastrointestinal tract (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue in females at 3, 6 and 9.3 g/kg/day), testes (hypospermia in the epididymides and seminiferous tubule degeneration or multiucleated spermatids of the testes) and salivary gland (atrophy). The NOAEL could not be determined as treatment-related findings were seen at all dose levels.

Study Title: 9-Month Oral (Gavage) Toxicity Study with Miralax PEG 3350 in Dogs

Key Study Findings: In a 9-month oral gavage study in dogs, animals were treated at 0.75, 1.5 and 3 g/kg/day. The target organs of toxicity appeared to be testes (retarded development) and prostate (lymphocyte infiltrate) in the males and mammary gland (glandular hyperplasia), liver (vacuolation) and gallbladder (lymphocyte infiltrate and epithelial hyperplasia) in females. The NOAEL could not be determined, as apparent treatment-related effects were seen at all tested doses.

Study No.: [redacted] 382012

Volume # Page #: 9.1, page 1

Conducting Laboratory and Location: [redacted]

Date of Study Initiation: July 24, 2002

GLP Compliance: A statement of compliance was included.

QA Report: yes (X) no ( )

Drug, Lot #, and % Purity: Miralax PEG 3350, Lot No. 1275, [redacted]

Methods:

Doses: 0.75, 1.5 and 3 g/kg/day

Basis of Dose Selection: The doses were selected based on the results of the previous 28-day study in dogs at 3, 6 and 9.3 g/kg/day.

Species/Strain: Dogs/Beagle

Number/Sex/Group or Time Point (Main Study): 4/sex/group

Route, Formulation, and Volume: Oral, solution in water, 10 ml/kg

Satellite Groups Used for Toxicokinetics or Recovery: None

Age: 6 months old

Weight: 8.5 to 9.9 kg

Study Design: The study design is shown in the table (from page 19 of the study report) below.

Group Number	Test Article	Dosage Level (g/kg/day)	Dosage Volume (mL/kg)	Number of Animals	
				Males	Females
1	Vehicle	0	10	4	4
2	MiraLax™ PEG-3350	0.75	10	4	4
3	MiraLax™ PEG-3350	1.5	10	4	4
4	MiraLax™ PEG-3350	3	10	4	4

Observation and Times:

Mortality: Mortality was observed twice daily.

Clinical Signs: Clinical signs were observed twice daily.

Body Weights: Body weights were recorded on a weekly basis.

Food Consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopy was conducted at Week -2, 19 and 38.

ECG: Electrocardiography was conducted at Week -2, 19 and 38.

Hematology: Hematology was examined at Week -2, 19 and 38.

Clinical Chemistry: Clinical chemistry was performed at Week -2, 19, 23 and 38.

Urinalysis: Urinalysis was conducted at Week -2, 19, 23 and 38.

Gross Pathology: Gross pathology was conducted at necropsy.

Organ Weights: The following organs were weighed from all animals at necropsy: adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary gland, prostate, spleen, testes, thyroid and parathyroid.

Histopathology: Histopathological examinations were conducted on the following tissues (table from page 31 of the study report) from all animals.

- Adrenal glands [cortex and medulla (2)]
- Aorta
- Bone with marrow
  - Femur
  - Sternum
- Bone marrow smear[a]
- Brain
  - Cerebellum level 1
  - Cerebellum level 2
  - Cerebrum with medulla/pons
- Epididymides (2)[b]
- Eyes with optic nerve (2)[c]
- Gallbladder
- Gastrointestinal tract
  - Esophagus
  - Stomach
  - Duodenum
  - Jejunum
  - Ileum
  - Cecum
  - Colon (descending)
  - Rectum
- Heart
- Kidneys (2)
- Liver (sections of two lobes)
- Lungs (including bronchi, fixed by inflation with fixative)
- Lymph nodes
  - Mandibular
  - Mesenteric
- Mammary gland (females only)
- Ovaries (2)
- Pancreas
- Peripheral nerve (sciatic)
- Pituitary
- Prostate
- Salivary glands [mandibular (2)]
- Skeletal muscle (rectus femoris)
- Skin
- Spinal cord (cervical, midthoracic, lumbar)
- Spleen
- Testes (2)[b]
- Thymus
- Thyroid [with parathyroids (2)][d]
- Tongue
- Trachea
- Urinary bladder
- Uterus with cervix
- Vagina
- Gross lesions (when possible)

Toxicokinetics: Blood samples for TK analysis were collected from all dogs on study days 0, 133 (week 19) and 271 (week 38) at 0, 0.5, 1, 2, 4, 8, and 24 hours post-dose.

Results:

Mortality: None

Clinical Signs: Treatment-related clinical findings included mucoid feces, soft feces and diarrhea at 0.75. 1.5 and 3 g/kg/day. Theses signs were observed in a dose-related manner prior to dosing and or one hour after dosing. The following table (from page 35 of the study report) shows the clinical signs.

Summary of Number of Occurrences of Selected Clinical Observations[a]

	Males				Females			
Dose Level (g/kg/day)	**0**	**0.75**	**1.5**	**3**	**0**	**0.75**	**1.5**	**3**
Diarrhea	6	59	398	945	10	80	439	685
Soft Feces[b]	48	232	483	168	21	278	374	226
Emesis[c]	26	43	28	77	46	66	53	69

Summary of Total % Findings of Selected Clinical Observations[d]

	Males				Females			
Dose Level (g/kg/day)	**0**	**0.75**	**1.5**	**3**	**0**	**0.75**	**1.5**	**3**
Diarrhea	0.3%	2.6%	17.8%	42.2%	0.4%	3.6%	19.6%	30.6%
Soft Feces[b]	2.1%	10.4%	21.6%	7.5%	0.9%	12.4%	16.7%	10.1%
Emesis[c]	1.2%	1.9%	1.3%	3.4%	2.1%	2.9%	2.4%	3.1%

[a] = Clinical observations for detailed physical examinations, prior to dosing and one hour post-dosing combined.
[b] = Soft feces observations include findings of soft feces and mucoid feces.
[c] = Emesis observations include findings of emesis containing white, yellow and/or food material.
[d] = The total percent findings of selected clinical observations equals the total number of clinical observations (*e.g.*, diarrhea) observed for each group divided by the total number of possible clinical observations made during the course of the study (2240 total possible scheduled observations).

Body Weights: The mean initial and final weight of control males were 9.9 and 13.4 kg, respectively. The mean initial and final weight of control females were 8.5 and 10.8 kg, respectively. There were no significant treatment-related effects.

Food Consumption: The mean initial and final food consumption in control males were 316 and 335 g/animal/day, respectively. The mean initial and final food consumption in control females were 280 and 299 g/animal/day, respectively. Food consumption was unaffected by treatment.

Ophthalmoscopy: No significant treatment-related effects were observed.

Electrocardiography: No significant test article-related effects were noted in the electrocardiographic data at the study week 19 and 38. However, at study week 38, several treated animals, and one control group female, had sinus tachycardia. The incidence of this finding was 0 of 4, 1 of 4, 1 of 4 and 1 of 4 for the control, 0.75, 1.5 and 3 g/kg/day group males, respectively, and 1 of 4, 1 of 4, 0 of 4 and 1 of 4 for the same respective female groups. In addition, several treated animals, and two control group females, had conduction disturbances. These conduction disturbances included intraventricular conduction disturbances (IVCD), left posterior arborization block (LPAB) and/or left anterior arborization block (LAAB). The combined incidence of these findings were 0 of 4, 0 of 4, 0 of 4 and 1 of 4 for the control, 0.75, 1.5 and 3 g/kg/day group males, respectively, and 2 of 4, 0 of 4, 1 of 4 and 1 of 4 for the same respective female groups. The following table shows the cardiographic incidences. These effects did not appear to be treatment-related in the absence of a clear dose-response and similar findings in the control animals.

Parameter	Males (n = 4)				Females (n = 4)			
	0 g/kg/d	0.75 g/kg/d	1.5 g/kg/d	3.0 g/kg/d	0 g/kg/d	0.75 g/kg/d	1.5 g/kg/d	3.0 g/kg/d
Interventricular conduction disturbance	4	3	3	3	2	3	3	2
Sinus tachycardia	0	1	1	1	1	1	0	1
Left posterior arborization block	0	0	0	1	1	0	0	1
Left anterior arborization block	0	0	0	0	1	0	0	0

Hematology: There were no significant treatment-related changes.

Clinical Chemistry: No significant treatment-related effects were observed.

Urinalysis: There were no significant treatment-related changes.

Gross Pathology: There were no significant test article-related macroscopic findings at the scheduled necropsies.

Organ Weights: Organ weights were unaffected by test article administration.

Histopathology: There were no significant test article-related microscopic findings. However, apparent dose-related trends in the incidence of immaturity of the testes and lymphoid infiltrates in the prostate were observed in males. These were not observed in any control male. Immature testes were primarily characterized by focal and usually unilateral aggregates of seminiferous tubules lined by Sertoli cells with a paucity or complete absence of germ cells. In addition, apparent dose-related trends in the incidences of mammary gland hyperplasia, hepatocellular vacuolar change and lymphoid

infiltrates of the gall bladder were observed in the females. The following table shows the histopathological changes.

Tissue Finding	Grade	Males (n = 4)				Females (n = 4)			
		0 g/kg/d	0.75 g/kg/d	1.5 g/kg/d	3.0 g/kg/d	0 g/kg/d	0.75 g/kg/d	1.5 g/kg/d	3.0 g/kg/d
Testes -Immature (juvenile development)	1	0	2	2	1	-	-	-	-
Prostate -Lymphocyte infiltrate	1	0	0	1	0	-	-	-	-
	2	0	0	0	2	-	-	-	-
Mammary gland -Hyperplasia, glandular	1	-	-	-	-	0	1	1	1
	3	-	-	-	-	0	0	1	0
Liver -Vacuolation	1	-	-	-	-	0	0	1	1
Gallbladder -Infiltrate, lymphocyte	1	-	-	-	-	1	2	2	3
-Hyperplasia, epithelial	2	-	-	-	-	0	0	0	1

1: Minimal
2: Mild
3: Moderate

Toxicokinetics: The exposures ($AUC_{0\text{-}24h}$) to PEG-3350 increased in a dose proportional manner over the dose range of 0.75 to 3 g/kg/day. No significant accumulation of PEG-3350 was observed in the plasma of either sex. There was no apparent gender difference in exposure to PEG 3350. The mean TK parameters are shown in the following table (from page 42 of the study report).

TOXICOKINETIC RESULTS

Gender/ PEG-3350 (g/kg/day)	PEG-3350 Results $AUC_{0\text{-}24}$ (ng-h/mL)			C_{max} (ng/mL)			t_{max} (h)		
	Day 0	Week 19	Week 38	Day 0	Week 19	Week 38	Day 0	Week 19	Week 38
Males									
0.75	14797	21530	11578	1353	2706	2320	3.5	4.3	2.5
1.5	21024	18089	17754	1703	2166	3832	6.0	3.3	2.0
3	41496	31775	28756	4830	3704	6170	2.8	4.0	2.0
Females									
0.75	11266	15543	15123	796	1702	2187	7.0	4.0	3.3
1.5	39542	21181	30934	4766	2525	4738	3.0	4.0	2.0
3	50312	48623	34396	8626	5228	5096	3.0	3.5	2.0

Summary: In a 9-month oral gavage study in dogs, animals were treated at 0.75, 1.5 and 3 g/kg/day. The target organs of toxicity appeared to be testes (retarded development) and prostate (lymphocyte infiltrate) in the males and mammary gland (glandular hyperplasia), liver (vacuolation) and gallbladder (lymphocyte infiltrate and epithelial hyperplasia) in females. The NOAEL could not be determined, as apparent treatment-related effects were seen at all tested doses.

2.6.6.4 Genetic toxicology

Study title: Ames assay

Key findings: Negative

Study no.: 21570

Volume #, and page #: 10.1, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: April 5, 2002
GLP compliance: A statement of compliance (OECD) was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: PEG 3350, Lot No. 1275, [redacted]

Methods

Strains/cell line: *Salmonella typhimurium* TA 1535, 1537, 98 and 100 and *Escherichia coli* WP2*uvra*

Doses used in definitive study: 17, 50, 167, 500, 1667 and 5000 µg/plate

Basis of dose selection: Toxicity

Negative controls: Water

Positive controls: +S9: 2-Aminoanthracene (0.5-20 µg/plate)
-S9: N-Ethyl-N-nitro-N-nitrosoguanidine (2 µg/plate), sodium azide (1 µg/plate), 2-Nitrofluorene (1 µg/plate), 9-aminoacridine (80 µg/plate).

Incubation and sampling times: 2-3 days

Results:

Study validity: Triplicate plates were used for each strain and colonies were counted manually. The following were the criteria for a positive response: 1) a dose-related increase in the number of revertants and/or 2) a reproducible biologically relevant positive response (TA 98, TA 1535, TA 1537 and WP2uvrA: the number of revertants was at least twice as high as compared to the spontaneous reversion rate or control. Strain TA 100: the number of revertants was at least 1.5 times higher than the control) for at least one of the test points in at least one strain with or without metabolic activation. The study was considered valid as it met all the criteria for a valid assay.

Study outcome: Negative. The results of the second mutation assay are shown in the following tables (from page 23 and 24 of the study report).

Table 3 Second Mutation Assay

Mean Number of Revertant Colonies Per Plate in the Presence of S9 Mix (FL 095)

Item	Dose Level µg per plate	TA 1535	TA 1537	TA 98	TA 100	WP2uvrA
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
WATER	100 µl	21 ± 5	15 ± 6	34 ± 2	149 ± 4	10 ± 1
PEG3350	17	19 ± 5	19 ± 4	30 ± 6	165 ± 12	10 ± 2
	50	23 ± 5	13 ± 3	26 ± 2	137 ± 2	10 ± 1
	167	18 ± 2	13 ± 4	30 ± 5	127 ± 12	7 ± 2
	500	17 ± 2	14 ± 4	29 ± 4	165 ± 11	6 ± 3
	1667	20 ± 3	14 ± 4	32 ± 6	137 ± 12	8 ± 6
	5000	15 ± 1	13 ± 6	33 ± 8	139 ± 6	11 ± 2
Positive controls	Compound	2AAN	2AAN	2AAN	2AAN	2AAN
	Dose Level µg per plate	2	2	0.5	0.5	20
	Mean ± SD	379 ± 18	249 ± 4	359 ± 16	683 ± 18	754 ± 14

SD Standard Deviation
2AAN 2-Aminoanthracene

Table 3 Second Mutation Assay

Mean Number of Revertant Colonies Per Plate in the Absence of S9 Mix ,

Item	Dose Level µg per plate	TA 1535	TA 1537	TA 98	TA 100	WP2uvrA
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
WATER	100 µl	18 ± 1	13 ± 3	20 ± 7	128 ± 5	9 ± 3
PEG3350	17	11 ± 4	16 ± 5	18 ± 1	101 ± 10	13 ± 4
	50	15 ± 5	14 ± 4	21 ± 4	111 ± 6	12 ± 2
	167	12 ± 3	15 ± 2	18 ± 2	118 ± 13	7 ± 2
	500	14 ± 3	15 ± 3	18 ± 3	118 ± 10	11 ± 1
	1667	14 ± 6	20 ± 3	22 ± 6	131 ± 9	12 ± 2
	5000	12 ± 2	13 ± 3	20 ± 7	124 ± 12	11 ± 4
Positive controls	Compound	NaN_3	9AA	2NF	NaN_3	ENNG
	Dose Level µg per plate	1	80	1	1	2
	Mean ± SD	578 ± 6	4201 ± 802	2749 ± 382	1190 ± 82	749 ± 26

SD Standard Deviation
NaN_3 Sodium azide
9AA 9-Aminoacridine
2NF 2-Nitrofluorene
ENNG N-Ethyl-N-nitro-N-nitrosoguanidine

Study title: Chromosome Aberrations Assay with Human Peripheral Lymphocytes

Key findings: Negative

Study no.: 21899

Volume #, and page #: 10.1, page 1

Conducting laboratory and location: [redacted]
Date of study initiation: April 5, 2002
GLP compliance: A statement of compliance was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: PEG 3350, Lot No. 1275, [redacted]

Methods:

Cell line: Human peripheral lymphocytes

Doses used in definitive study: 313, 625, 1250, 2500 and 5000 µg/ml

Basis of dose selection: Cytotoxicity and osmolality

Negative controls: RPM 1640 medium

Positive controls: Cyclophosphamide (+S9, 10-40 µg/ml) and mitomycin C (-S9, 0.01-0.5 µg/ml)

Incubation and sampling times: The following table (from page 12 of the study report) shows the treatment schedule for this study.

S9 Mix	Cultures Established	Test	Treatment Period	Recovery Period(Includes 1 h wash)	Colcemid	Harvest
Presence of S9 mix	*ca* 48 h before exposure	Tests 1 and 2	0-5 h	5-26 h	26-29 h	29 h
Absence of S9 mix		Test 1	0-5 h	5-26 h	26-29 h	29 h
		Test 2	0-25 h	25-26 h	26-29 h	29 h
				25-50 h	50-53 h	53 h

Results:

Study validity: Treatments with test item or vehicle control substances were performed on duplicate cell cultures. Based on cytotoxicity and osmolality, 3 concentrations were selected for assessment of chromosomal aberrations. From 2-4 slides per culture, up to 50 metaphase cells per slide, a total of 100 metaphase cells per culture were examined. The study was considered valid for the following reasons: there was no evidence of contamination, cells in the vehicle control had normal growth, the results of vehicle and positive control were as expected and the test article had 3 acceptable dose levels for assessment. The response at a single dose was considered as significant if the percent of

aberrant cells was consistently greater than double the vehicle control. In addition, a test item was considered positive if both Test 1 and 2 were found positive.

Study outcome: Negative. The results of test 1 and 2 are shown in the following table.

Test 1

S9 Mix	Treatment (µg/ml)	No. of Cells Analyzed	TAG (Mean %, n = 2)	TA (Mean %, n =2)	Mitotic Index (Mean, n =2)
Yes (5 h treatment, 29 h harvest)	RPM 1640	100	0.01	1.0	1.0
	625	100	0.005	0.5	0.975
	2500	100	0.00	0.0	0.58
	5000	100	0.5	0.5	0.525
	CP 20	100	8	7	
	CP 40	100	8	4	
No (5 h treatment, 29 h harvest)	RPM 1640	100	1.0	0.5	1.0
	625	100	0.0	0.0	0.915
	2500	100	0.5	0.5	1.34
	5000	100	0.5	0.5	1.37
	CP 20	100	2.0	2	-
	CP 40	100	11.0	10	-

Test 2:

S9 Mix	Treatment (µg/ml)	No. of Cells Analyzed	TAG (Mean %, n = 2)	TA (Mean %, n = 2)	Mitotic Index (Mean, n = 2)
Yes (5 h treatment, 29 h harvest)	RPM 1640	100	1.0	1.0	1.0
	625	100	0.0	0.0	1.16
	2500	100	3.5	3.5	1.31
	5000	100	0.5	0.5	1.09
	CP 20	100	11	10	-
	CP 40	100	18	17	-
No (5 h treatment, 29 h harvest)	RPM 1640	100	2.5	1.5	1.0
	625	100	0.5	0.5	1.165
	2500	100	1.5	1.5	1.28
	5000	100	1.5	1.0	1.33
	CP 20	100	4.0	3	-
	CP 40	100	7.0	6	-

TA: Total aberrant cells excluding gap
TAG: Total aberrant cells including gap

Study title: *In Vivo* Oral Bone Marrow Micronucleus Assay in Rats

Key findings: Negative. In this study, the animals were treated orally (gavage) at 0 and 24 h at 2000 mg/kg. The percentage of micronucletaed polychromatic erythrocytes (MN-PCE) was 0.06%, 0.09% and 2.53% in the control, PEG 3350 and positive control group, respectively. The frequencies of MN-PCE in the PEG 3350 treated group were 0.11% and 0.13% in males and females, respectively. The historical control range was 0.01-0.12% for 5-6 rats. The increase in frequency in the PEG 3350 treated group compared to control was not statistically significant and within the historical control value and was not considered as positive.

Study no.: 768779

Volume #, and page #: 10.1, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: April 30, 2002
GLP compliance: A statement of compliance was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: PEG 3350, Lot No. 1275, [redacted]

Methods:

Strains/species: Sprague Dawley/Rats

Doses used in definitive study: Animals (n = 10/sex) were dosed at 0 and 24 h at 2000 mg/kg (10 ml/kg).

Basis of dose selection: The doses were selected based on the results of a dose ranging study at 50, 125, 350, 800 and 2000 mg/kg in rats (n = 1/sex/dose). There were no mortality in the dose ranging study and 2000 mg/kg/day dose was selected for the micronucleus test.

Negative controls: Water (n = 5/sex)

Positive controls: Cyclophosphamide (50 mg/kg, oral, n = 5 male rats)

Sampling times: Blood samples were collected for micronucleus analysis at 48 hour post-treatment.

Results:

Study validity: Two slides were prepared from each animal. Approximately 2000 polychromatic erythrocytes (PCE) per animal were scored for micronuclei and for the frequency of micronucleated PCEs (MN-PCE). The test was considered positive if an increase greater than 10% over the expected historical control. The increase should be

statistically significant relative to concurrent and historical control frequency for MN-PCE. It is to be mentioned here that the sponsor has tested only one dose (2000 mg/kg at 0 and 24 h) in this study.

Study outcome: Negative. The percentage of MN-PCE was 0.06%, 0.09% and 2.53% in the control, PEG 3350 and positive control group, respectively. The frequencies of MN-PCE in the PEG 3350 treated group were 0.11% and 0.13% in males and females, respectively. The historical control range was 0.01-0.12% for 5-6 rats. The increase in frequency in the PEG 3350 treated group compared to control was not statistically significant and within the historical control value and did not meet the criteria for a positive response and the result was considered negative. The following table (from page 25 of the study report) shows the study outcome.

PEG3350
Micronucleus Test in Bone Marrow of CD Rats
Table 4 Summary of Assessment Data

Treatment	Dose (h)	Sex	No. of Rats Scored	Erythrocytes				
				Normochromatic Cells (NCE)	Polychromatic Cells (PCE)			PCE/NCE
				No. of MN-NCE	PCE Analysed	No. of MN-PCE	% MN-PCE	Mean ± S.D.
10 ml water $kg^{-1}.day^{-1}$	0 + 24	♂	5	5	10013	6	0.06	0.97 ± 0.13
		♀	5	4	10014	6	0.06	0.89 ± 0.06
		♂♀	10	9	20027	12	0.06	0.93 ± 0.10
2000 mg PEG3350 kg^{-1} day^{-1}	0 + 24	♂	5 (a)	7	10010	11	0.11	0.79 ± 0.04
			4 (b)	5	8006	3	0.04	0.93 ± 0.03
			9 (a+b)	12	18016	14	0.08	0.85 ± 0.08 (*)
		♀	5 (a)	6	10014	13	0.13 *i*	0.93 ± 0.04
			5 (b)	4	10009	7	0.07	0.95 ± 0.04
			10 (a+b)	10	20023	20	0.10	0.94 ± 0.04
		♂♀	19 (a+b)	22	38039	34	0.09 (ns)	0.90 ± 0.08
50 mg Cyclophosphamide. kg^{-1} day^{-1}	0 + 24	♂	5	46 α	10017	253	2.53 Φ	0.60 ± 0.07

a = main group
b = contingency group
PCE = Polychromatic erythrocytes
MN-PCE = Micronucleated PCE
NCE = Normochromatic erythrocytes
MN-NCE = Micronucleated NCE
Φ = Positive response in PCE
α = Evident response in NCE
i = Inconclusive response (from historical data)
ns = not statistically different from vehicle control group
* = statistically significant difference from vehicle control group

2.6.6.5 Carcinogenicity

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

Review of Mouse Carcinogenicity Study

P/T REVIEWER: Tamal K. Chakraborti, Ph.D.
DATE:

NDA: 22-015
DRUG CODE#: None
CAS#: 25322-68-3
DIVISION: Division of Gastroenterology Products
DRUG NAME: Miralax™ (Polyethylene glycol (PEG) 3350, NF Powder for Solution)

SPONSOR: Braintree Laboratories, Inc.
LABORATORY: [redacted]
MOUSE CARCINOGENICITY STUDY REPORT DATE: November 4, 2005

THERAPEUTIC CATEGORY: Laxative
PHARMACOLOGICAL CLASSIFICATION: Osmotic laxative
MUTAGENIC/GENOTOXIC: No.

MOUSE CARCINOGENICITY STUDY:

MOUSE STUDY DURATION (weeks): 104 Weeks
STUDY STARTING DATE: May 15, 2003
STUDY ENDING DATE: November 4, 2005
MOUSE STRAIN: [redacted]:CD-1®(ICR) BR
ROUTE: Oral (Gavage)
DOSING COMMENTS: Dose selection was based on data from a 3-month oral toxicity study ([redacted] Research Study No. [redacted]-382011) with PEG 3350 at 1.5, 3 and 6 g/kg/day. In that study, soft feces were observed with the highest incidence at 6 g/kg/day group. In addition, minimal to mild dilation and mucosal attenuation was observed microscopically in the gastrointestinal tract of the 6 g/kg/day group. The dose levels for this study were approximately 6.25, 12.5 and 25 times greater than the ED_{90} (0.24 g/kg/day for a 70 kg person) in humans. In addition, the dose volume was 10 ml/kg/day, allowed for the maximum amount of test article for dosing as a weight-to-volume mixture where the formulation was still considered a solution at room temperature. The solubility coefficient for the test article in water at room temperature was 0.62 g/ml. The highest dose of 6 g/kg/day was thus considered as the maximum feasible dose (MFD). The high dose selection based on the MFD appeared to be appropriate and acceptable.

NUMBER OF MICE:
- Control (C): 60/sex
- Low Dose (LD): 60/sex
- Middle Dose (MD): 60/sex
- High Dose-1 (HD): 60/sex

MOUSE DOSE LEVELS* (g/kg/day):
- Low Dose: 1.5
- Middle Dose: 3
- High Dose-1: 6

*: Each group initially consisted of 65 animals/sex/group; 5 additional mice/sex/group were added to accommodate the potential for accidental deaths in young mice. Following 4 weeks of dosing, animals were selected at random for elimination from the study to achieve the target group size of 60 animals/sex/group. Dose administration was discontinued for the 6 g/kg/day group females on 11 March 2005 (study week 94), when survival reached the protocol-specified survival of 20 animals in any group. All male groups and the control, 1.5 and 3 g/kg/day group females were dosed for 104 weeks and the 6 g/kg/day group females were maintained without dosing until study week 104.

BASIS FOR DOSES SELECTED: MFD

PRIOR FDA DOSE CONCURRENCE: None

MOUSE CARCINOGENICITY: Negative

MOUSE TUMOR FINDINGS: No test article-related increase in neoplasms was observed at any dose level of Miralax PEG 3350. However, there was a statistically significant increase (8 of 60 females) in benign tumors (adenomas) in the Harderian gland of females at 3 g/kg/day compared to control (1 of 60 females). This finding was not considered treatment-related in the absence of a dose-response.

MOUSE STUDY COMMENTS: In this study, PEG 3350 was administered by oral gavage as a solution in the vehicle, deionized water, for up to 104 weeks to 3 groups (Groups 2-4) of CD-1 mice (n = 60/sex/dose) at 1.5, 3 and 6 g/kg/day. A concurrent control group (Group 1) received the vehicle on a comparable regimen. Dose administration was discontinued for the 6 g/kg/day group females on study week 94, when survival reached the protocol-specified survival of 20 animals in any group. All male groups and the control, 1.5 and 3 g/kg/day group females were dosed for 104 weeks and the 6 g/kg/day group females were maintained without dosing until study week 104. For males and females, there was at least 23 and 26 animals/group, respectively, which were treated through week 92 of the study. Therefore, exposure to the test article was considered adequate and the generalized decrease in survival did not appear to have a negative impact on the study outcome. The high dose selection was based on the MFD appeared to be appropriate and acceptable. Overall, the conduct of the study appeared to be adequate and acceptable.

There was no test article-related significant increase in neoplasms at any dose level of PEG 3350. However, there was a statistically significant increase (8 of 60 females) in the number of benign tumors (adenomas) in the Harderian gland of females at 3 g/kg/day when compared to control (1 of 60 females). However, this observation was not considered as treatment-related in the absence of a dose-response. Overall, there appeared to be no treatment-related tumor findings in this study.

COVER SHEET FOR CARCINOGENICITY STUDY IN THE MOUSE

1. **Study Number:** [redacted]-382018
2. **Name of Laboratory:** [redacted]
3. **Mouse Strain:** [redacted]:CD-1®(ICR) BR
4. **No./Sex/Group:** 60
5. **Doses (0, L, M, and H):** 0 (deionized water), 1.5, 3 and 6 g/kg/day
6. **Basis for Dose Selection Stated:** Maximum feasible dose (MFD)
7. **Interim Sacrifice:** None
8. **Total Duration (Weeks):** 104 Weeks
9. **Week/Site for First Tumor:** The following table shows week/site for first tumor incidences in males and females.

TREATMENT	MALE	FEMALE
Control	51/Malignant lymphoma: multiple sites	70/Histiocytic sarcoma: multiple sites
1.5 g/kg/day (PEG 3500)	28/Malignant lymphoma: multiple sites	28/Sarcoma: sternum
3.0 g/kg/day (PEG 3500)	41/Hemangioma: lymph node	52/Histiocytic sarcoma: multiple site
6.0 g/kg/day (PEG 3500)	54/Granular cell tumor, benign, epididymides; carcinoma: thyroid	39/Hemangiosarcoma: uterus

10. **Number Alive at Termination:** The survival data is shown in the following table (from page 51 of Vol. 11.1 of the study report).

Text Table 2: Survival at Study Weeks 25, 51, 77, 85 and 104 - Number and Percentage of Animals Surviving

	MALES				FEMALES			
Group (g/kg/day)	0	1.5	3	6	0	1.5	3	6
Study Week								
25	60/60 100%	60/60 100%	60/60 100%	60/60 100%	58/59[a] 98%	60/60 100%	59/59[a] 100%	60/60 100%
51	57/59[a] 97%	56/60 93%	54/58[a] 93%	55/60 92%	57/59[a] 97%	56/60 93%	56/59[a] 95%	59/60 98%
77	52/59[a] 88%	44/60 73%	41/58[a] 71%	38/60 63%	47/59[a] 80%	42/60 70%	45/58[a] 71%	40/60 67%
84	45/59[a] 76%	40/60 67%	38/58[a] 66%	33/60 55%	45/59[a] 76%	36/60 60%	38/58[a] 66%	30/60 50%
104	28/59[a] 47%	15/59[a] 25%	19/58[a] 33%	19/59[a] 32%	29/59[a] 49%	21/60 35%	22/57[a] 39%	13/60 22%

[a] = Mortality data corrected for accidental deaths.
NA = Not Applicable

11. Statistical Methods Used:

Mortality data: Kaplan-Meier estimates of group survival rates were calculated by sex. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pair-wise comparisons of each test article-treated group with the control group. In addition, a log-rank dose-response trend test of survival rates was also performed including the control group and 3 test article-treated groups.

Tumor data: The principal statistical method used to evaluate tumor incidence and data interpretation of possible carcinogenic effects was linear trend analysis by the method of Peto et al (1980). The mortality-prevalence method of Peto was performed without continuity correction, incorporating the context (incidental or fatal) in which tumors were observed. The fatal context was used for a tumor discovered at death that was considered the cause of death (directly or indirectly), while the incidental context was used for a tumor discovered at death or at a scheduled euthanasia. The following fixed intervals were used for incidental tumor analyses: study weeks 0-52, 53-78, 79-92, 93-end of study and scheduled terminal euthanasia.

Tumors were characterized as malignant, benign or as a metastatic site, by tissue or organ affected and by cell of origin. Each diagnosed tumor type was analyzed separately and analysis of combined tumor types was performed as described by McConnell (1986). For organs in which an exhaustive examination of animals was planned [Harderian glands (females only), kidneys, tissue masses and gross for all animals in all dose groups], the incidence of each tumor type was analyzed

with a one-sided trend test. In addition, pair-wise comparisons with the control group were conducted for each active treatment group. For organs in which an exhaustive examination of animals was planned only for the control and high-dose groups, the incidence of each tumor type was analyzed with a one-sided pair-wise comparison of the control group with the high dose group. Pair-wise comparisons were performed only for other tumor types (for which all animals were not examined). Systemic tumors were analyzed by one-sided trend test (all groups), as well as pair-wise comparisons. The systemic tumor types detected in the study were malignant lymphoma, histiocytic sarcoma, hemangioma, hemangiosarcoma, mesothelioma, granulocytic leukemia and malignant fibrous histiocytoma.

An exact permutation test was conducted for analyses with low tumor incidence. Low tumor incidence was defined as one in which the marginal incidence rate within a defined interval was 4 or less. Statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.005 and 0.025 significance levels for common and rare tumors, respectively. Pair-wise comparisons with the control group were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. Common tumors were defined as those with a spontaneous rate of 1% or more in the concurrent control group and/or the [redacted] historical control database; rare tumors were defined as those with a spontaneous rate of less than 1% in the concurrent control group and/or the [redacted] historical control database.

12. **Attach Tumor and Non-Tumor Data for Each Tissue**: List of neoplastic and non-neoplastic lesions is attached in Appendix-1.

CARCINOGENICITY:

Study Title: 104-Week Oral (Gavage) Carcinogenicity Study with Miralax PEG 3350 in CD-1 Mice

Key Study Findings:

- There was a test article-related decrease in survival for males and females (statistically significant at 1.5 and 6 g/kg/day groups) when compared to the control group by the end of the study. All groups had 50% or higher survival through study week 88 for males and study week 84 for females. Dose administration in the 6 g/kg/day female group was discontinued during study week 94, when the survival reached the protocol-specified survival of 20 animals within any group and these females were maintained without treatment through study week 104. At week 104, survival in the control, 1.5, 3 and 6 g/kg/day groups was 47%, 25%, 33% and 32%, respectively, for males and 49%, 35%, 39% and 22%, respectively for females. For males and females, there was at least 23 and 26 animals/group, respectively, which were treated through week 92 of the study. Therefore, exposure to the test article was considered adequate and the generalized decrease in survival did not appear to have a negative impact on the study outcome.

- An increased incidence of soft feces was noted in the 3 and 6 g/kg/day group males and females.

- There were no test article-related effects on body weights or food consumption. The incidence of palpable masses was unaffected by test article administration. There were no test article-related effects on hematology parameters.

- Non-neoplastic microscopic observations included test article-related increased incidence of renal amyloidosis at 6 g/kg/day in females that died or were euthanized *in extremis* compared to the control group animals that died or were euthanized *in extremis*.

- There were no treatment-related tumor findings in any tissue in either sex.

Adequacy of the Carcinogenicity Study and Appropriateness of the Test Model: The dose selection based on the MFD appeared to be appropriate and acceptable. At week 104, survival in the control, 1.5, 3 and 6 g/kg/day groups was 47%, 25%, 33% and 32%, respectively, for males and 49%, 35%, 39% and 22%, respectively for females. For males and females, there was at least 23 and 26 animals/group, respectively, which were treated through week 92 of the study. Therefore, exposure to the test article was considered adequate and the generalized decrease in survival did not appear to have a negative impact on the study outcome. The selected route of administration was oral (gavage) as this is the intended route of human clinical exposure. The animal model, the :CD-1(ICR) BR mouse was considered as appropriate for chronic and carcinogenicity

studies and is a widely used strain for which significant historical control data are available.

Evaluation of Tumor Findings: There were no significant treatment-related tumor findings in any tissue. However, there was a statistically significant increase (8 of 60 females) in benign tumors (adenomas) in the Harderian gland of females at 3 g/kg/day compared to control (1 of 60 females). However, this was not observed at highest dose. This finding was not considered treatment-related in the absence of a dose-response. Overall, the results appeared to be negative for any tumor findings.

Study No.: [redacted]-382018
Volume #, and Page #: Vol. 11.1, page 1
Conducting Laboratory and Location: [redacted]
Date of Study Initiation: May 15, 2003
GLP Compliance: A statement of compliance was included.
QA Report: yes (X) no ( )
Drug, Lot #, and % Purity: Miralax PEG 3350, Lot No. 1274 and 1275, [redacted]
CAC Concurrence: None

Methods:

Doses: 1.5, 3 and 6 g/kg/day. The following table (from page 33 of Vol. 11.1 of sponsor's submission) shows the study design.

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals[a] Males	Females
1	Vehicle	0	0	10	65	65
2	MiraLax™ PEG-3350	1.5	0.15	10	65	65
3	MiraLax™ PEG-3350	3	0.3	10	65	65
4	MiraLax™ PEG-3350	6	0.6	10	65	65

[a] = The target group size was 60 animals/sex/group. Five additional animals/sex/group were added to accommodate the potential for dosing accidents. After 4 weeks of dosing, animals were selected at random for elimination from the study such that there were 60 animals/sex/group. During the first 4 weeks of the study, 1 male and 1 female in the control group were euthanized in extremis and 1 male in the 6 g/kg/day group and 1 female each in the control and 1.5 g/kg/day groups were found dead. These animals were considered culled animals. The culled animals were subject to a gross necropsy and full tissues were retained for possible future analysis. Data collected from these animals are presented in Appendix F.

Basis of dose selection (MTD, MFD, AUC etc.): MFD
Species/strain: Mouse/[redacted]:CD-1®(ICR) BR
Number/sex/group (main study): 60/sex/dose
Route, formulation, volume: Oral, solution, 10 ml/kg

Frequency of dosing: Daily
Satellite groups used for toxicokinetics or special groups: None
Age: 44-46 days old
Animal housing: All animals were housed individually in wire-mesh cages.
Restriction paradigm for dietary restriction studies: None
Drug stability/homogeneity: The test article was stored at room temperature and was considered stable at room temperature. The test article formulations for each dose level were stored in the refrigerator (0^0-10^0C). Stability analyses of test article formulations demonstrated that refrigerated test article formulations were stable over a minimum period of 17 days at concentrations spanning the range of expected concentrations for this study.
Dual controls employed: No
Interim sacrifices: None
Deviations from original study protocol: There are minor protocol deviations. Theses protocol deviations did not appear to have any significant impact on the quality or integrity of the data nor on the outcome of the study.

Observation Times

Mortality: Animals were observed for mortality twice daily.

Clinical signs: Clinical signs were examined twice daily.
Body weights: Body weights were recorded weekly, beginning approximately 1 week prior to the initiation of dose administration (study week -1), through study week 14 and biweekly thereafter.

Food consumption: Food consumptions were recorded weekly, beginning approximately 1 week prior to the initiation of dose administration (study week -1), through study week 14 and biweekly thereafter.

Hematology and Clinical Chemistry: Blood samples were collected for hematology and clinical chemistry at scheduled necropsy.

Histopathology: Microscopic examination was performed on all tissues listed below (from page 41 of sponsor's study report) from all animals found dead or euthanized *in extremis* and all animals in the control and 6 g/kg/day groups at the primary necropsy. Tissue masses, kidneys, Harderian gland (females only) and gross lesions were also examined from all animals in the 1.5 and 3 g/kg/day groups.

Adrenal glands (2)
Aorta (thoracic)
Bone with marrow
  Femur
  Sternum
Bone marrow smear[a]
Brain
  Cerebrum level 1
  Cerebrum level 2
  Cerebellum with medulla/pons
Clitoral glands (2)
Epididymides (2)[b]
Eyes with optic nerve (2)[c]
Exorbital lacrimal gland (2)
Gallbladder
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Harderian glands (2)
Heart
Kidneys (2)
Liver
Lungs (including bronchi, fixed by inflation with fixative)
Lymph nodes
  Mandibular (2)
  Mesenteric
Mammary gland
Ovaries with oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Preputial glands (2)
Prostate
Salivary glands [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin (inguinal)
Spinal cord
  Cervical
  Mid-thoracic
  Lumbar
Spleen
Testes (2)[b]
Thymus (if present)
Thyroid [both lobes with parathyroids (2)][d]
Tongue
Trachea
Urinary bladder (inflated with fixative)
Uterus with cervix
Vagina
Zymbal's gland (2)
All gross lesions (including masses)

[a] - Bone marrow smears were obtained at necropsy but not placed in formalin; slides were not collected from animals that were found dead.
[b] - Preserved in Bouin's solution
[c] - Preserved in Davidson's solution
[d] - Parathyroid glands were examined microscopically if they were in the plane of section of the thyroid and in all cases when a gross lesion was present.

Toxicokinetics: None.

Results:

Mortality: Treatment-related decrease in survival was observed for males and females at all dose levels by the end of the study. A statistically significant trend for decreased survival was noted for all female groups as well as a statistically significant decrease in survival for the 1.5 and 6 g/kg/day group females was observed when compared to the control group at the scheduled necropsy. Although there were no statistically significant differences in survival among males, the overall number of surviving males at the scheduled necropsy were lower than (1.5 g/kg/day), similar to (3 g/kg/day) or higher than (6 g/kg/day) the respective female groups while the number of surviving control group animals were similar (28 males and 29 females). Therefore, the decreased survival in the treated males was considered test article-related. The following table shows the survival data (from page 51 of the sponsor's study report).

Text Table 2: Survival at Study Weeks 25, 51, 77, 85 and 104 - Number and Percentage of Animals Surviving

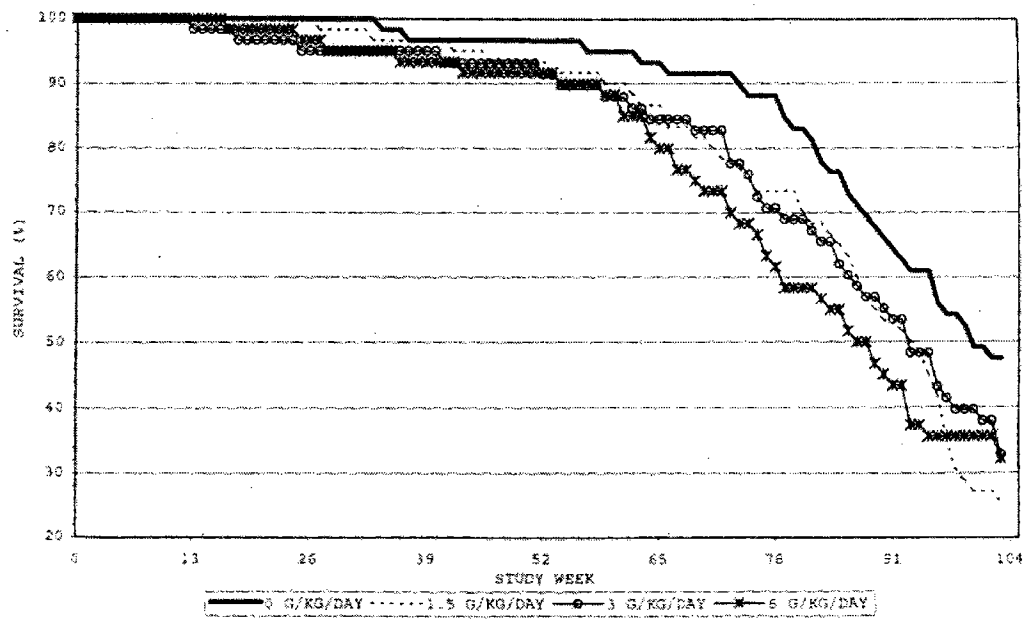
	MALES				FEMALES			
Group (g/kg/day)	0	1.5	3	6	0	1.5	3	6
Study Week								
25	60/60 100%	60/60 100%	60/60 100%	60/60 100%	58/59[a] 98%	60/60 100%	59/59[a] 100%	60/60 100%
51	57/59[a] 97%	56/60 93%	54/58[a] 93%	55/60 92%	57/59[a] 97%	56/60 93%	56/59[a] 95%	59/60 98%
77	52/59[a] 88%	44/60 73%	41/58[a] 71%	38/60 63%	47/59[a] 80%	42/60 70%	45/58[a] 71%	40/60 67%
84	45/59[a] 76%	40/60 67%	38/58[a] 66%	33/60 55%	45/59[a] 76%	36/60 60%	38/58[a] 66%	30/60 50%
104	28/59[a] 47%	15/59[a] 25%	19/58[a] 33%	19/59[a] 32%	29/59[a] 49%	21/60 35%	22/57[a] 39%	13/60 22%

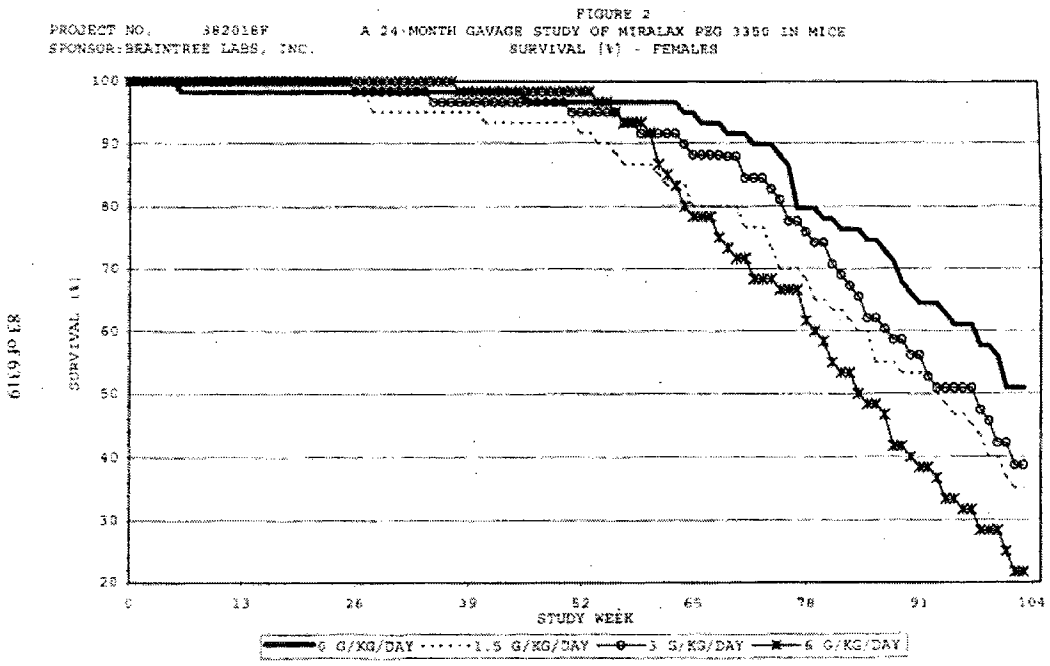
[a] = Mortality data corrected for accidental deaths.
NA = Not Applicable

The survival curves (from page 82 and 83 of study report) are shown below.

Appears This Way
On Original

FIGURE 1
PROJECT NO. [redacted]-382018N A 24-MONTH GAVAGE STUDY OF MIRALAX PEG 3350 IN MICE
SPONSOR:BRAINTREE LABS, INC. SURVIVAL (%) - MALES





Clinical signs: Treatment-related increased incidence of soft feces was observed at 3 and 6 g/kg/day group males and females. This finding was more prevalent in the females at the affected doses compared to the males.

Palpable Mass: There were no treatment-related changes.

Body weights: The mean initial and final body weight of control males was 30.0 and 37.7 g, respectively. The mean initial and final body weight of control females was 23.0 and 34.1 g, respectively. There were no treatment-related effects on body weights. The body weight curves are shown below (from page 84 and 85 of the study report).

FIGURE 3
PROJECT NO. [redacted] 382018N A 24-MONTH GAVAGE STUDY OF MIRALAX PEG 3350 IN MICE
SPONSOR:BRAINTREE LABS. INC. BODY WEIGHTS (G) - MALES

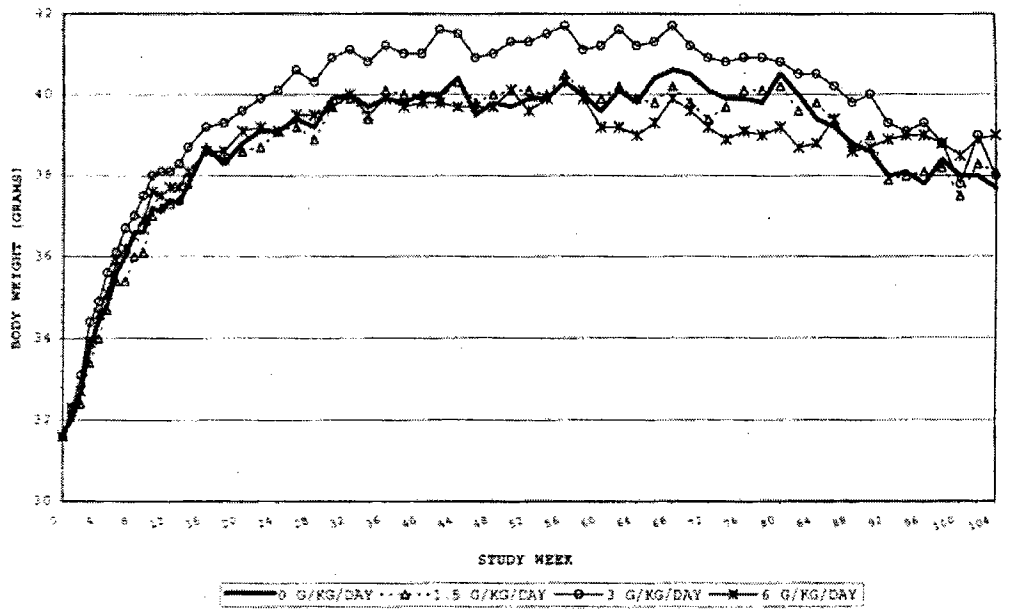
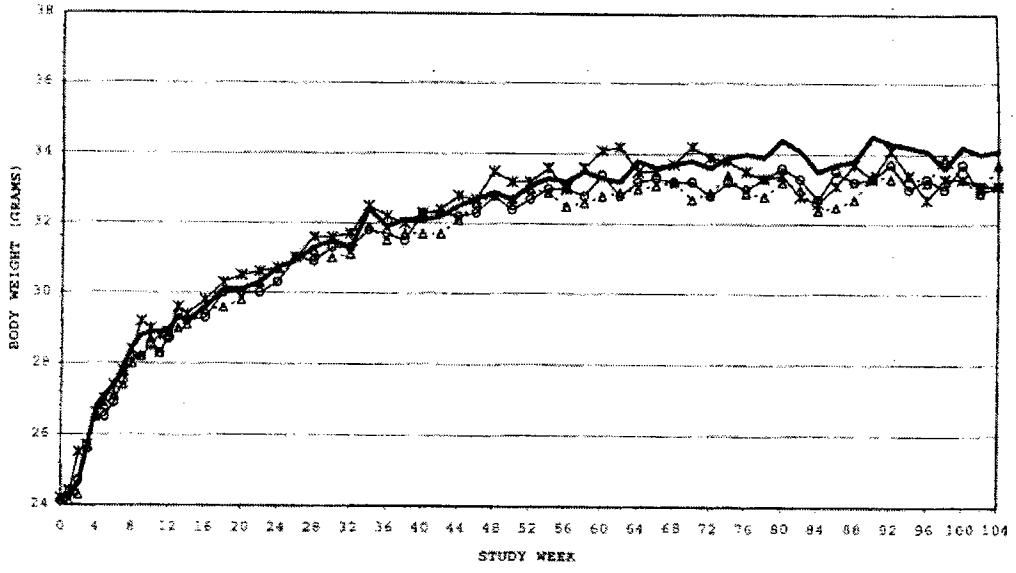


FIGURE 4
PROJECT NO. [redacted] 382018F A 24-MONTH GAVAGE STUDY OF MIRALAX PEG 3350 IN MICE
SPONSOR:BRAINTREE LABS. INC. BODY WEIGHTS (G) - FEMALES



The following table shows the body weight data.

Week	Males (Dose: g/kg/day)					Females (Dose: g/kg/day)				
	0	1.5	3	6		0	1.5	3	6	
Initial	30.0	29.9	30.1	30.0		23.0	23.0	23.2	23.2	
13	37.3	37.4	38.3	37.7		29.3	29.0	29.4	29.6	
26	39.4	39.2	40.6	39.5		30.9	31.0	31.0	31.0	
52	39.9	40.1	41.3	39.6		33.1	33.0	32.7	33.2	
104	37.7	38.1	38.0	39.0		34.1	33.7	33.1	33.1	
Body Weight (% of Control)										
Final Week	100.0	101.1	100.7	103.4		100.0	98.8	97.1	97.1	

Food consumption: The mean initial and final food consumption in control males was 5.7 and 5.6 g/animal/day, respectively. The mean initial and final food consumption in control females was 5.4 and 5.4 g/animal/day, respectively. There were no test article-related effects on food consumption.

Hematology and Clinical Chemistry: There were no significant treatment-related changes.

Gross pathology: No significant treatment-related changes were observed.

Histopathology:

Non-neoplastic: Treatment-related histopathological changes were observed in the kidney (amyloidosis). The following table shows the incidence of amyloidosis in the kidney (from page 56 of the study report).

Text Table 4: Incidence of Amyloidosis in the Kidney

	Males				Females			
Dose Level (g/kg/day)	0	1.5	3	6	0	1.5	3	6
Unscheduled Deaths	12/32	16/45	7/41	9/40	9/31	15/39	13/38	25/47
Scheduled Necropsy	0/28	2/15	2/19	4/19	9/29	5/21	3/22	5/13
Combined	12/60	18/60	9/60	13/59	18/60	20/60	16/60	30/60

Neoplastic: No treatment-related increase in neoplasms was observed at any of the tested dose level of Miralax PEG 3350. However, there was a statistically significant increase in the number of benign tumors (adenomas) in the Harderian gland at 3 g/kg/day female group. However, this was not considered as treatment-related in the absence of a dose-response. The following table (from page 57 of the study report) shows the neoplastic incidences in the Harderian gland.

Text Table 5: Neoplastic Incidence of Harderian Gland

	Males				Females			
Dose Level (g/kg/day)	0	1.5	3	6	0	1.5	3	6
Adenoma (benign)								
Unscheduled Deaths	3/31	1/45	2/41	1/41	0/31	1/39	4/38	3/47
Scheduled Necropsy	5/28	NA	1/2	5/19	1/29	0/21	4/22	0/13
Combined	8/59	1/45	3/43	6/60	1/60	1/60	8/60*	3/60
Carcinoma								
Unscheduled Deaths	0/31	0/45	0/41	0/41	0/31	0/39	0/38	0/47
Scheduled Necropsy	1/28	NA	0/2	0/19	1/29	1/21	0/22	0/13
Combined	1/59	0/45	0/43	0/60	1/60	1/60	0/60	0/60

* - Statistically significant at p = 0.0042

The following summary tables (from pages 15-23 of study report) show the tumor findings.

-382018
Braintree Laboratories, Inc.

MiraLax™ PEG-3500

SUMMARY TABLE

Carcinogenicity	Study Title: A 24-Month Oral (Gavage) Carcinogenicity Study of MiraLax™ PEG-3500 in Mice								Test Article: MiraLax™ PEG-3500		Page 1
Species/Strain: CD-1®(ICR) BR mice	Duration of Dosing: 94 weeks (6 g/kg/day females), 104 weeks (all male groups and control, 1.5 and 3 g/kg/day females)								Study No. 382018		
Initial Age: 8 weeks	Method of Administration: Oral gavage										
Date of First Dose: 20 May 2003 (females), 23 July 2003 (males)	Vehicle/Formulation: Deionized water								GLP Compliance: Yes		
	Treatment of Controls: Deionized water										
Basis for High-Dose Selection: Results of previous toxicology studies.											
Special Features: Up to 5mice/sex/group culled at study week 4.											
Dosage (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Number of Animals											
At Start	65	65	65	65	65	65	65	65			
Culled (or died/euthanized by Week 4)	5	5	5	5	5	5	5	5			
Died/Euthanized or Moribund[a]	31	30	44	39	39	35	40	47			
Accidental Deaths	1	1	1	0	2	3	1	0			
Terminal Euthanasia (Week 104)	28	29	15	21	19	22	19	13			
Survival[b]											
Ratio (alive/no. in group)	28/59	29/59	15/59	21/60	19/58	22/57	19/59	13/60			
Percentage	47%	49%	25%	35%	33%	39%	32%	22%			
Body Weight (%[c])											
At 6 Months	39.9 g	33.1 g	↑0.5	↓0.3	↑3.5	↓1.2	↓0.8	↑0.3			
End of Study	37.7 g	34.1 g	↑1.1	↓1.1	↑0.8	↓2.9	↑3.4	↓2.9			
Food Consumption (%[c])											
At 6 Months	5.6 g/day	5.4 g/day	↓1.8	↑5.6	↑5.4	0.0	↑1.8	↑1.9			
End of Study	5.6 g/day	5.1 g/day	↓3.6	↑2.0	↓1.8	0.0	↑3.6	↑3.9			

a = Does not include accidental deaths
b = Percent survival based on number of animals surviving through the last full week prior to necropsy. Culled animals and accidental deaths were excluded from survival calculations.
c = For controls, group means are shown. For treated groups, percent differences from the control group are shown.

[redacted]382018
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MiraLax™ PEG-3500

SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted]-382018 (continued)										Page 2
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60			
Animals with Neoplastic Findings:											
Adrenal cortex (no. examined)[e]	59	59	44	40	40	35	57	60			
Adenoma, A cell	1	1	0	0	0	0	1	1			
Adenoma	0	1	0	0	0	0	0	0			
Adrenal Medulla (no. examined)[e]	56	44	39	40	35	27	53	53			
Pheochromocytoma, benign	1	0	0	1	0	0	0	1			
Pheochromocytoma, malignant	0	0	0	0	1	0	0	0			
Bone (no. examined)[e]	1	3	NA	NA	1	0	NA	0			
Osteosarcoma	0	1	NA	NA	1	0	NA	0			
Brain (no. examined)[e]	59	59	44	39	39	35	59	60			
Sarcoma, meningeal	0	0	0	0	0	1	0	0			
Cervix (no. examined)[e]	NA	59	NA	39	NA	37	NA	55			
Carcinoma, squamous cell	NA	1	NA	0	NA	0	NA	0			
Granular cell tumor, benign	NA	0	NA	1	NA	0	NA	0			
Fibroma	NA	1	NA	0	NA	1	NA	0			
Leiomyoma	NA	0	NA	1	NA	1	NA	0			
Leiomyosarcoma	NA	1	NA	0	NA	0	NA	0			
Sarcoma, endometrial stromal	NA	0	NA	0	NA	1	NA	0			
Epididymides (no. examined)[e]	59	NA	42	NA	39	NA	59	NA			
Granular cell tumor, benign	0	NA	0	NA	0	NA	1	NA			
Harderian glands (no. examined)[e]	58	59	44	60	41	57	59	60			
Adenoma	8	1	1	1	3	8	6	3			
Adenoma, multiple	2	0	0	0	0	0	1	0			
Carcinoma	1	1	0	1	0	0	0	0			

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. 382018 (continued)										Page 3
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60			
Animals with Neoplastic Findings:											
Kidneys (no. examined)[e]	59	59	59	60	58	57	58	60			
Adenoma, renal tubule	0	0	2	0	1	0	1	0			
Carcinoma, renal tubule	1	0	0	0	0	0	0	0			
Renal mesenchymal tumor, malignant	0	0	0	0	0	1	0	0			
Liver (no. examined)[e]	59	59	46	43	44	39	59	60			
Adenoma, hepatocellular	12	2	1	1	7	0	5	1			
Adenoma, hepatocellular, multiple	3	0	0	0	1	0	1	0			
Carcinoma, hepatocellular	4	0	3	0	3	0	4	0			
Lipoma	0	0	0	0	0	1	0	0			
Lungs (no. examined)[e]	59	59	47	43	42	44	59	60			
Adenoma, bronchiolo-alveolar	6	6	6	3	9	8	10	4			
Adenoma, bronchiolo-alveolar, multiple	2	0	2	0	2	2	2	1			
Carcinoma, bronchiolo-alveolar	4	6	4	1	5	4	4	6			
Mammary gland (no. examined)[e]	1	53	0	37	0	32	1	55			
Adenocarcinoma	0	1	0	0	0	1	0	2			

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. -382018 (continued)										Page 4
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60			
Animals with Neoplastic Findings:											
Ovaries (no. examined)[e]	NA	53	NA	53	NA	52	NA	60			
Adenoma, tubulostromal	NA	2	NA	0	NA	0	NA	0			
Cystadenoma	NA	0	NA	1	NA	2	NA	2			
Granulosa cell tumor, benign	NA	1	NA	0	NA	0	NA	0			
Granulosa cell tumor, malignant	NA	0	NA	1	NA	0	NA	0			
Leiomysarcoma	NA	0	NA	0	NA	1	NA	0			
Luteoma	NA	1	NA	0	NA	0	NA	0			
Teratoma, benign	NA	0	NA	1	NA	0	NA	0			
Thecoma, malignant	NA	0	NA	0	NA	1	NA	0			
Pancreas (no. examined)[e]	59	58	43	40	39	35	58	60			
Adenoma, islet cell	1	0	0	0	0	0	0	0			
Carcinoma, islet cell	0	0	0	0	0	1	0	0			
Pituitary (no. examined)[e]	55	57	43	39	37	36	56	57			
Adenoma, pars distalis	0	1	0	2	0	1	0	0			
Carcinoma, pars distalis	0	0	0	0	0	0	1	0			
Skin (no. examined)[e]	59	59	46	39	40	38	58	60			
Pilomatricoma	0	0	0	0	0	0	0	2			
Sarcoma, undifferentiated	0	0	0	1	1	1	0	1			
Spleen (no. examined)[e]	59	59	44	47	39	37	59	60			
Sarcoma, undifferentiated	0	0	0	0	0	0	1	0			
Sternum (no. examined)[e]	59	59	44	38	39	35	59	60			
Sarcoma, undifferentiated	0	0	0	1	0	0	0	0			

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted]-382018 (continued)								Page 5
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6		
Gender	M	F	M	F	M	F	M	F	
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60	
Animals with Neoplastic Findings:									
Stomach, glandular (no. examined)[e]	59	59	43	39	39	35	59	60	
Neuroendocrine cell tumor, malignant	0	0	0	0	0	0	1	0	
Polyp	0	1	0	0	0	0	0	0	
Stomach, nonglandular (no. examined)[e]	59	59	44	39	39	36	59	60	
Papilloma, squamous cell	0	0	0	0	0	1	0	0	
Systemic tumors (no. examined)[e]	12	29	7	29	14	24	10	28	
Fibrous histiocytoma, malignant	0	0	0	0	0	0	0	1	
Leukemia, granulocytic	0	0	0	2	0	0	0	0	
Lymphoma, malignant	5	13	1	10	2	8	4	12	
Sarcoma, histiocytic	1	5	0	9	2	9	2	4	
Hemangiosarcoma	4	4	5	5	5	6	3	6	
Hemangioma	2	9	1	5	5	3	3	6	
Mesothelioma, malignant	1	0	0	0	0	0	0	0	
Testes (no. examined)[e]	59	NA	43	NA	44	NA	59	NA	
Adenoma, interstitial cell	0	NA	1	NA	0	NA	0	NA	
Thyroid gland (no. examined)[e]	59	59	44	38	38	35	58	60	
Adenoma, follicular cell	0	0	0	0	0	0	1	0	
Carcinoma, follicular cell	1	0	1	0	0	0	1	0	
Urinary bladder (no. examined)[e]	58	59	45	39	40	35	58	60	
Submucosal mesenchymal tumor	0	0	1	1	0	0	0	0	

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted]-382018 (continued)										Page 6
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60			
Animals with Neoplastic Findings:											
Uterus (no. examined)[e]	NA	59	NA	58	NA	55	NA	60			
Carcinoma	NA	3	NA	2	NA	2	NA	1			
Granular cell tumor, benign, multiple	NA	0	NA	1	NA	0	NA	0			
Leiomyoma	NA	1	NA	1	NA	1	NA	1			
Leiomyosarcoma	NA	3	NA	2	NA	0	NA	0			
Polyp, endometrial stromal	NA	4	NA	7	NA	5	NA	6			
Polyp, endometrial stromal, multiple	NA	0	NA	0	NA	1	NA	0			
Sarcoma, endometrial stromal	NA	1	NA	1	NA	1	NA	0			
Metastatic sites:											
Adrenal Medulla (no. examined)[e]	56	44	39	40	35	27	53	53			
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	0	1	0	0			
Aorta (no. examined)[e]	58	59	44	38	38	35	59	58			
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	0	1	0	0			
Bone (no. examined)[e]	1	3	NA	NA	1	1	NA	1			
Carcinoma, bronchiolo-alveolar; lung	0	0	NA	NA	0	0	NA	1			
Epididymides (no. examined)[e]	59	NA	42	NA	39	NA	59	NA			
Carcinoma, bronchiolo-alveolar; lung	0	NA	0	NA	1	NA	0	NA			
Femur (no. examined)[e]	59	59	44	40	39	35	59	60			
Osteosarcoma	0	1	0	0	0	0	0	0			

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted]-382018 (continued)										Page 7
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60			
Animals with Neoplastic Findings:											
Metastatic sites:											
Heart (no. examined)[e]	59	59	44	39	39	35	59	60			
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	1	1	0	1			
Kidneys (no. examined)[e]	59	59	59	60	58	57	58	60			
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	1	0	0	1			
Liver (no. examined)[e]	59	59	46	43	44	39	59	60			
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	1	1	0	0			
Osteosarcoma; bone	0	1	0	0	0	0	0	0			
Sarcoma, undifferentiated; skin	0	0	0	0	0	0	0	1			
Sarcoma, undifferentiated; spleen	0	0	0	0	0	0	1	0			
Lungs (no. examined)[e]	59	59	47	43	42	44	59	60			
Adenocarcinoma; mammary gland	0	0	0	0	0	0	0	1			
Osteosarcoma; bone	0	1	0	0	1	0	0	0			
Sarcoma, undifferentiated; skin	0	0	0	0	0	0	0	1			
Lymph node, mediastinal (no. examined)[e]	NA	7	1	7	2	4	5	9			
Carcinoma, bronchiolo-alveolar; lung	NA	0	0	0	1	1	0	1			
Sarcoma, undifferentiated; skin	NA	0	0	0	0	0	0	1			
Lymph node, tr/b (no. examined)[e]	NA	NA	NA	NA	NA	3	NA	1			
Carcinoma, bronchiolo-alveolar; lung	NA	NA	NA	NA	NA	1	NA	0			
Marrow, femur (no. examined)[e]	59	59	44	39	39	34	59	60			
Sarcoma, undifferentiated; spleen	0	0	0	0	0	0	1	0			

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. 382018 (continued)									
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6			
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60		
Animals with Neoplastic Findings:										
Metastatic sites:										
Pancreas (no. examined)[c]	59	58	43	40	39	35	58	60		
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	1	0	0	0		
Skeletal muscle (no. examined)[c]	59	59	44	39	39	35	59	60		
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	0	0	0	1		
Osteosarcoma; bone	0	0	0	0	1	0	0	0		
Soft tissue, cer (no. examined)[c]	NA	NA	NA	NA	NA	NA	NA	1		
Carcinoma, bronchiolo-alveolar; lung	NA	NA	NA	NA	NA	NA	NA	1		
Soft tissue, thorax (no. examined)[c]	1	NA	NA	NA	NA	NA	NA	1		
Carcinoma, bronchiolo-alveolar, multiple; lung	0	NA	NA	NA	NA	NA	NA	1		
Spleen (no. examined)[c]	59	59	44	42	39	37	59	60		
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	0	0	0	1		
Stomach, glandular (no. examined)[c]	59	59	43	39	39	35	59	60		
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	1	0	0	1		
Skeletal muscle (no. examined)[c]	59	59	44	39	39	35	59	60		
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	0	0	0	1		
Osteosarcoma; bone	0	0	0	0	1	0	0	0		

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
c = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

[redacted]-382018 MiraLax™ PEG-3500
Braintree Laboratories, Inc.

SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted]-382018 (continued)								Page 9
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6		
Total Number of Animals in Group[d]	M: 59	F: 59	M: 59	F: 60	M: 58	F: 57	M: 59	F: 60
Animals with Neoplastic Findings:								
Metastatic sites:								
Thymus (no. examined)[e]	50	52	38	38	37	33	55	58
Carcinoma, bronchiolo-alveolar; lung	0	0	0	0	0	1	0	0
Urinary bladder (no. examined)[e]	58	59	45	39	40	35	58	60
Carcinoma; uterus	0	0	0	1	0	0	0	0

NA = not applicable
d = Number of animals adjusted by removal of culled animals and accidental deaths.
e = Number of animals differs from number of animals in group due to examination of target tissues, gross lesions in the 1.5 and 3 g/kg/day groups and tissues that were too autolyzed to be examined.

The sponsor stated that adenomas of the Harderian gland were considered common in mice (Botts S et al., 1999. In Pathology of the Mouse; Marompot, R.R., Boorman G.A., Gaul, B.W., Eds.; Cache River Press: Vienna, IL; p 67) and a broad range of incidence for this lesion was observed for [redacted]:CD-1(ICR) BR mice, 1.67% to 18.64% and 1.35% to 8.33% for males and females, respectively, in the historical control data compiled by [redacted] This finding did not appear to be treatment-related in the absence of a dose response. Overall, the results of this study appeared to be negative for any tumor findings.

Toxicokinetics: None

Summary: In a 104-week oral (gavage) carcinogenicity study in CD-1 mice, animals (n = 60/sex/group) were treated with Miralax PEG 3350 at 0 (water), 1.5, 3 and 6 g/kg/day (10 ml/kg). There was a treatment-related decrease in survival for males and females (statistically significant at 1.5 and 6 g/kg/day groups) when compared to the control group by the end of the study. Dose administration in the 6 g/kg/day female group was discontinued during study week 94, when the survival reached the protocol-specified survival of 20 animals within any group and these females were maintained without treatment through study week 104. At week 104, survival in the control, 1.5, 3 and 6 g/kg/day groups was 47%, 25%, 33% and 32%, respectively, for males and 49%, 35%, 39% and 22%, respectively for females. Treatment-related clinical signs included soft feces at 3 and 6 g/kg/day group males and females. There were no test article-related effects on body weights or food consumption. The incidence of palpable masses was unaffected by test article administration. There were no significant test article-related effects on hematology or clinical chemistry parameters. Non-neoplastic microscopic observations included test article-related increased incidence of renal amyloidosis at 6 g/kg/day in females that died or were euthanized *in extremis* compared to the control group animals that died or were euthanized *in extremis*. There were no significant tumor findings in any tissue that could be attributed to treatment with Miralax PEG 3500.

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

Review of Rat Carcinogenicity Study

P/T REVIEWER: Tamal K. Chakraborti, Ph.D.
DATE:

NDA: 22-015
DRUG CODE#: None
CAS#: 25322-68-3
DIVISION: Division of Gastroenterology Products
DRUG NAME: Miralax™ (Polyethylene glycol (PEG) 3350, NF Powder for Solution)

SPONSOR: Braintree Laboratories, Inc.
LABORATORY: [redacted]
RAT CARCINOGENICITY STUDY REPORT DATE: April 20, 2005

THERAPEUTIC CATEGORY: Laxative
PHARMACOLOGICAL CLASSIFICATION: Osmotic laxative
MUTAGENIC/GENOTOXIC: No.

RAT CARCINOGENICITY STUDY:

RAT STUDY DURATION (weeks): 104 Weeks
STUDY STARTING DATE: July 1, 2002
STUDY ENDING DATE: April 20, 2005
RAT STRAIN: [redacted] :CD®(SD)IGS BR
ROUTE: Oral gavage
DOSING COMMENTS: Dose selection was based on the data obtained from a 3-month oral toxicity study in rats with Miralax PEG 3350 at dose levels of 1.5, 3 and 6 g/kg/day. In that study, there were no test article-related findings at any dose level. In addition, the high dose at 6 g/kg/day was, administered using the dose volume of 10 ml/kg/day, allowed for the maximum amount of test article for dosing as a weight-to-volume mixture where the formulation was still considered a solution at room temperature. The solubility coefficient for the test article in water at room temperature was 0.62 g/mL. The highest dose of 6 g/kg/day was considered as the maximum feasible dose (MFD). In this study, chronic toxicity was evaluated following treatment for first 26 weeks of the study and the report was presented separately.

NUMBER OF RATS:
- Control (C): 50/sex/group
- Low Dose (LD): 50/sex/group
- Middle Dose (MD): 50/sex/group
- High Dose (HD): 50/sex/group

RAT DOSE LEVELS* (g/kg/day):
- Low Dose: 1.5
- Middle Dose: 3.0
- High Dose: 6.0

(*Dose administration was discontinued for the 3 and 6 g/kg/day group females on May 22, 2004 (study week 98), when the survival reached the protocol-specified survival of 20 animals in any group. The control and 1.5 g/kg/day female groups continued to be dosed until study week 103. All surviving females in each group were euthanized during study week 103, when the protocol-specified survival of 15 animals was reached in the 3 g/kg/day female group. All the male groups were dosed for 104 weeks.)

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible): MFD

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): None

RAT CARCINOGENICITY (conclusion: negative; positive; MF; M; F): Negative

RAT TUMOR FINDINGS: No test article-related increase in neoplasms was observed at any dose level of Miralax PEG 3350. There were no statistically significant increases in any tumors when compared to the control group. One female at 3 g/kg/day group had a

renal tubular adenoma. Based on its single occurrence, this tumor was not considered test article-related.

RAT STUDY COMMENTS: In this study, Miralax PEG 3350 was administered by oral gavage as a solution in the vehicle, deionized water, for up to 104 weeks to 3 groups (Groups 2-4) of SD rats (n = 50/sex/group) at 1.5, 3 and 6 g/kg/day (10 ml/kg). A concurrent control group (Group 1) received the vehicle on a comparable regimen. Dose administration was discontinued for the 3 and 6 g/kg/day group females on May 22, 2004 (study week 98), when the survival reached the protocol-specified survival of 20 animals in any group. The control and 1.5 g/kg/day female groups continued to be dosed until study week 103. All surviving females in each group were euthanized during study week 103, when the protocol-specified survival of 15 animals was reached in the 3 g/kg/day female group. The decreased survival in females did not appear to have any negative impact on the data interpretation or study results, as sufficient number of animals were available at the end of week 103. All the male groups were dosed for 104 weeks. The high dose selection based on the MFD appeared to be appropriate and acceptable. Overall, the conduct of the study appeared to be adequate and acceptable. There were no test article-related significant increases in neoplasms at any dose level of PEG 3350. Overall, there appeared to be no treatment-related tumor findings in this study.

COVER SHEET FOR CARCINOGENICITY STUDY IN THE RAT

1. **Study Number:** [redacted]-3820009
2. **Name of Laboratory:** [redacted]
3. **Rat Strain:** [redacted]:CD®(SD) IGS BR
4. **No./Sex/Group:** 50
5. **Doses (0, L, M, and H):** 0 (deionized water), 1.5, 3 and 6 g/kg/day
6. **Basis for Dose Selection Stated:** MFD
7. **Interim Sacrifice:** 26 week for chronic toxicity
8. **Total Duration (Weeks):** 104 Weeks
9. **Week/Site for First Tumor:** The following table shows week/site for first tumor incidences in males and females.

TREATMENT	MALE	FEMALE
Control	58/Adenoma, benign: pars distalis (pituitary)	62/Adenocarcinoma, malignant: mammary gland
1.5 g/kg/day (PEG 3500)	28/Adenoma, benign: pars distalis (pituitary)	52/Adenoma, benign: pars distalis (pituitary)
3.0 g/kg/day (PEG 3500)	36/Malignant lymphoma: multiple sites	36/Sertoli cell tumor, benign: ovary C-Cell adenoma, benign: thyroid gland Liposarcoma, malignant: lymph node
6.0 g/kg/day (PEG 3500)	54/Adenoma, benign: pars distalis (pituitary)	55/Fibroadenoma, benign: mammary adenoma, benign: pars distalis (pituitary)

10. **Number Alive at Termination:** The survival data is shown in the following table (from page 51 of Vol. 12.1 of the study report).

Text Table 1: Survival at Study Weeks 25, 51, 77, 85, 102 and 103 - Number and Percentage of Animals Surviving

	MALES				FEMALES			
GROUP (G/KG/DAY)	0	1.5	3	6	0	1.5	3	6
STUDY WEEK								
25[a]	62/64[b] 97%	62/65 95%	62/65 95%	62/65 95%	65/65 100%	64/65 98%	63/64[b] 98%	60/61[b] 98%
51	49/50 98%	47/50 94%	48/49[b] 98%	49/49[b] 100%	50/50 100%	47/49[b] 96%	47/49[b] 96%	50/50 100%
77	40/50 80%	39/50 78%	43/49[b] 88%	42/49[b] 86%	41/50 82%	34/48[b] 71%	36/47[b] 77%	36/50 72%
85	39/50 78%	36/50 72%	39/49[b] 80%	36/49[b] 73%	36/50 72%	31/48[b] 65%	31/47[b] 66%	30/50 60%
103[c]	20/50 40%	20/50 40%	24/49[b] 49%	25/49[b] 51%	22/50 44%	19/48[b] 40%	15/47[b] 32%	18/50 36%
104[d]	20/50 40%	19/50 38%	24/49[b] 49%	25/49[b] 51%	NA	NA	NA	NA

[a] = Last week prior to the study week 26 interim necropsy.
[b] = Mortality data corrected for accidental deaths.
[c] = Data from the study week 103 primary necropsy for females.
[d] = Data from the study week 104 primary necropsy for males.
NA = Not Applicable

11. **Statistical Methods Used:**

Mortality data: Kaplan-Meier estimates of group survival rates were calculated by sex. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pair-wise comparisons of each test article-treated group with the control group. The pair-wise comparisons were made using Bonferroni test. In addition, a log-rank dose-response trend test of survival rates was also performed including the control group and 3 test article-treated groups.

Tumor data: The principal statistical method used to evaluate tumor incidence and data interpretation of possible carcinogenic effects was linear trend analysis by the method of Peto (Peto *et al.* 1980). The following fixed intervals were used for incidental tumor analyses: study weeks 0-50, 51-80, 81-end of the study and scheduled terminal euthanasia.

Tumors were characterized as malignant, benign or as a metastatic site, by tissue or organ affected and by cell of origin. Each diagnosed tumor type was analyzed separately and analysis of combined tumor types was performed as described by McConnell *et al.* (1986). For organs in which an exhaustive examination of animals was planned (all animals in all dose groups), the incidence of each tumor

type was analyzed with a one-sided trend test. In addition, pair-wise comparisons with the control group were conducted for each active treatment group. For organs in which an exhaustive examination of animals was planned only for the control and high-dose groups, the incidence of each tumor type was analyzed with a one-sided pair-wise comparison of the control group with the high dose group. Pair-wise comparisons with the control group were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. Common tumors were defined as those with a spontaneous rate of 1% or more in the concurrent control group and/or the [redacted] historical control database; rare tumors were defined as those with a spontaneous rate of less than 1% in the concurrent control group and/or the [redacted] historical control database.

12. **Attach Tumor and Non-Tumor Data for Each Tissue**: List of neoplastic and non-neoplastic lesions is attached in Appendix-2.

CARCINOGENICITY:

Study Title: 104-Week Oral (Gavage) Carcinogenicity Study with Miralax PEG 3350 in Rats

Key Study Findings:

In a 104-week oral (gavage) carcinogenicity study in SD rats, animals (n = 50/sex/group) were treated with Miralax PEG 3350 at 0 (water), 1.5, 3 and 6 g/kg/day (10 ml/kg). There was no significant impact on overall survival. Clinical signs included increased incidences of soft feces and brown material (dry and/or wet) on the urogenital and/or anogenital areas at 3 and 6 g/kg/day group males and the 1.5, 3 and 6 g/kg/day group females. Treatment-related histopathological changes were observed in the kidney (chronic progressive nephropathy, vacuolation, hyperplasia of clear cell and tubule cell), urinary bladder (cytoplasmic vacuolation of the superficial transitional cell layer), colon (glandular atrophy associated with dilatation), adrenal medulla (hyperplasia) and liver (basophilic and clear cell foci). There were no treatment-related tumor findings in any tissue in either sex. Overall, the results appeared to be negative for tumor findings.

Adequacy of the Carcinogenicity Study and Appropriateness of the Test Model: The dose selection based on the MFD appeared to be appropriate and acceptable. The selected route of administration was oral (gavage) as this is the intended route of human clinical exposure. The animal model, the [redacted] :CD(SD) IGS BR rats was considered as appropriate for chronic and carcinogenicity studies and is a widely used strain for which significant historical control data are available.

Evaluation of Tumor Findings: No test article-related increases in neoplasms were observed at any dose level of Miralax PEG 3350. There were no statistically significant increases in any tumors when compared to the control group. One female at 3 g/kg/day group had a renal tubular adenoma. Based on its single occurrence, this tumor was not considered test article-related. Overall, the results appeared to be negative for any tumor findings.

Study No.: [redacted] -382009
Volume #, and Page #: Vol. 12.1, page 1
Conducting Laboratory and Location: [redacted]
Date of Study Initiation: July 1, 2002
GLP Compliance: A statement of compliance was included.
QA Report: yes (X) no ( )
Drug, Lot #, and % Purity: Miralax PEG 3350, Lot No. 1275, [redacted] .
CAC Concurrence: None

Methods:

Doses: 1.5, 3 and 6 g/kg/day. The following table (from page 36 of the study report) shows the study design.

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals	
					Males	Females
1	Vehicle	0	0	10	50	50
2	MiraLax™ PEG-3350	1.5	0.15	10	50	50
3	MiraLax™ PEG-3350	3	0.3	10	50	50
4	MiraLax™ PEG-3350	6	0.6	10	50	50

Basis of dose selection (MTD, MFD, AUC etc.): MFD
Species/strain: Rat - CD(SD) IGS BR
Number/sex/group (main study): 50/sex/dose
Route, formulation, volume: Oral, solution, 10 ml/kg
Frequency of dosing: Daily
Satellite groups used for toxicokinetics or special groups: None
Age: 7 weeks
Animal housing: All animals were housed individually in wire-mesh cages.
Drug stability/homogeneity: Samples (10 mL each) from each formulation, including the vehicle, were collected at the time of the test article formulation on study weeks 0, 1, 2, 3, 8, 12, 25, 38, 51, 64, 76, 90 and 103 and were analyzed for concentration. Samples were also collected during study weeks 48 and 49 for concentration analysis of the 1.5 and 6 g/kg/day formulations only. All analyses were conducted by the [redacted] The test article formulations were found to contain the amounts of test article specified in the protocol (within 10% of the target concentrations) and, therefore, met the acceptance criteria.
Dual controls employed: No
Interim sacrifices: 26 week for 6-month toxicity study
Deviations from original study protocol: There are minor protocol deviations. These protocol deviations did not appear to have any significant impact on the quality or integrity of the data nor on the outcome of the study.

Observation Times

Mortality: Animals were observed for mortality twice daily.

Clinical signs: Clinical signs were examined twice daily.

Palpable mass: All animals were examined weekly for the presence of palpable masses.

Body weights: Body weights were recorded biweekly.

Food consumption: Food consumptions were recorded biweekly.

Hematology and clinical chemistry: Blood samples were collected for hematology and clinical chemistry at scheduled necropsy.

Ophthalmic examinations: Ocular examinations were conducted on all animals prior to the initiation of dose administration, prior to the interim necropsy (study week 25) and for all surviving males prior to the primary necropsy (study week 104). The females did not have ocular examinations conducted because a board-certified ophthalmologist was not available during the study week 103 necropsy.

Macroscopic examinations: A complete necropsy was conducted on all animals.

Histopathology: Microscopic examination was performed on all tissues listed below (from page 43 of the study report) from all animals euthanized *in extremis* or found dead, and from all animals in the control and 6 g/kg/day groups at the primary necropsy. In addition, tissue masses, liver, adrenal glands (cortex and medulla), colon, kidneys, urinary bladder and gross lesions were also examined from all animals in the 1.5 and 3 g/kg/day groups.

Adrenal glands (2)
Aorta
Bone with marrow
  Femur
  Sternum
Bone marrow smear[a]
Brain
  Cerebrum level 1
  Cerebrum level 2
  Cerebellum with medulla/pons
Clitoral glands (2)
Epididymides (2)[b]
Eyes with optic nerve (2)[c]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Harderian glands (2)
Heart
Kidneys (2)
Lacrimal glands
  Exorbital (2)
Liver (sections of two lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph nodes
  Mandibular (2)
  Mesenteric
Mammary gland (females only)
Nasal turbinates[d]
Ovaries with oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin (inguinal)
Spinal cord (cervical, midthoracic, lumbar)
Spleen
Testes (2)[b]
Thymus (if present)
Thyroid [both lobes with parathyroids, if present (2)]
Tongue
Trachea
Urinary bladder (inflated with fixative)
Uterus with cervix
Vagina
Zymbal's gland
All gross lesions (including masses)

[a] = Bone marrow smears were obtained at the scheduled necropsies but not placed in formalin
[b] = Preserved in Bouin's solution
[c] = Preserved in Davidson's solution
[d] = Levels I and III were examined microscopically according to the method of Young (1981).

Toxicokinetics: None.

Results:

Mortality: There were no significant treatment-related effects on survival. In both sexes, there were no statistically significant differences in survival rates. All groups had 50% or higher survival through study week 97 for males and 91 for females (98 and 92 weeks,

respectively). In males at week 104, the survival in the control, 1.5, 3 and 6 g/kg/day groups was 40%, 38%, 49% and 51%, respectively. In females at week 103, the survival in the control, 1.5, 3.0 and 6.0 g/kg/day was 44%, 40%, 32% and 36%, respectively. Treatment in the 3 and 6 g/kg/day female groups was discontinued during study week 98, when the survival reached the protocol-specified survival of 20 animals within any group. All the surviving females in each group were then euthanized during study week 103, when the protocol-specified survival of 15 animals was reached in the 3 g/kg/day female group. Survival data is shown in the following table (from page 51 of the study report).

Text Table 1: Survival at Study Weeks 25, 51, 77, 85, 102 and 103 - Number and Percentage of Animals Surviving

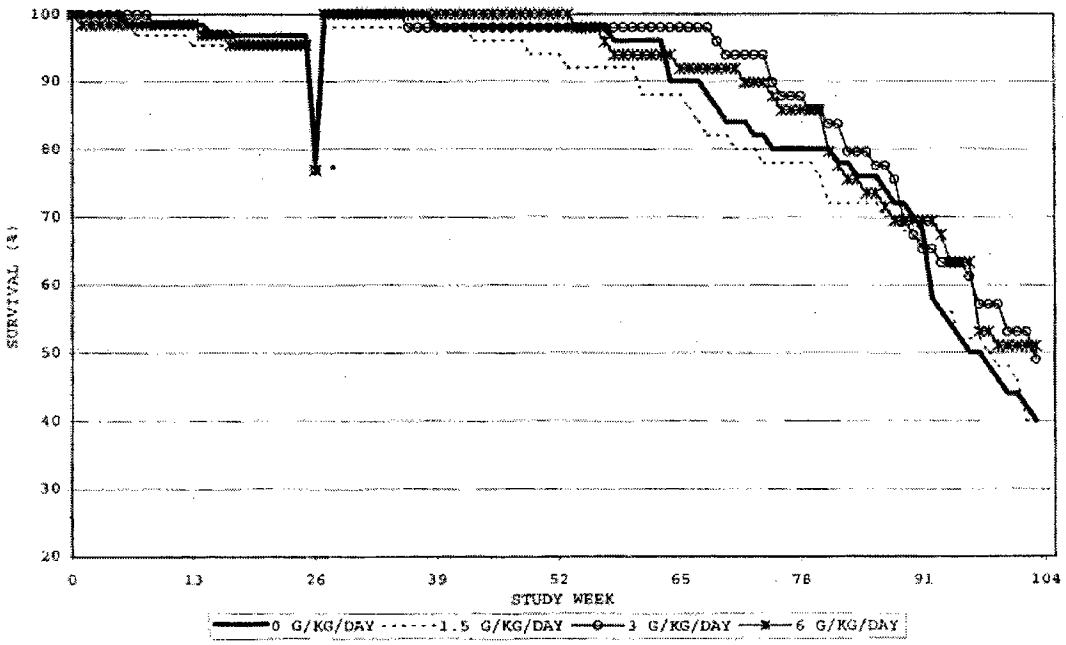
	MALES				FEMALES			
GROUP (G/KG/DAY)	0	1.5	3	6	0	1.5	3	6
STUDY WEEK								
25[a]	62/64[b] 97%	62/65 95%	62/65 95%	62/65 95%	65/65 100%	64/65 98%	63/64[b] 98%	60/61[b] 98%
51	49/50 98%	47/50 94%	48/49[b] 98%	49/49[b] 100%	50/50 100%	47/49[b] 96%	47/49[b] 96%	50/50 100%
77	40/50 80%	39/50 78%	43/49[b] 88%	42/49[b] 86%	41/50 82%	34/48[b] 71%	36/47[b] 77%	36/50 72%
85	39/50 78%	36/50 72%	39/49[b] 80%	36/49[b] 73%	36/50 72%	31/48[b] 65%	31/47[b] 66%	30/50 60%
103[c]	20/50 40%	20/50 40%	24/49[b] 49%	25/49[b] 51%	22/50 44%	19/48[b] 40%	15/47[b] 32%	18/50 36%
104[d]	20/50 40%	19/50 38%	24/49[b] 49%	25/49[b] 51%	NA	NA	NA	NA

[a] = Last week prior to the study week 26 interim necropsy.
[b] = Mortality data corrected for accidental deaths.
[c] = Data from the study week 103 primary necropsy for females.
[d] = Data from the study week 104 primary necropsy for males.
NA = Not Applicable

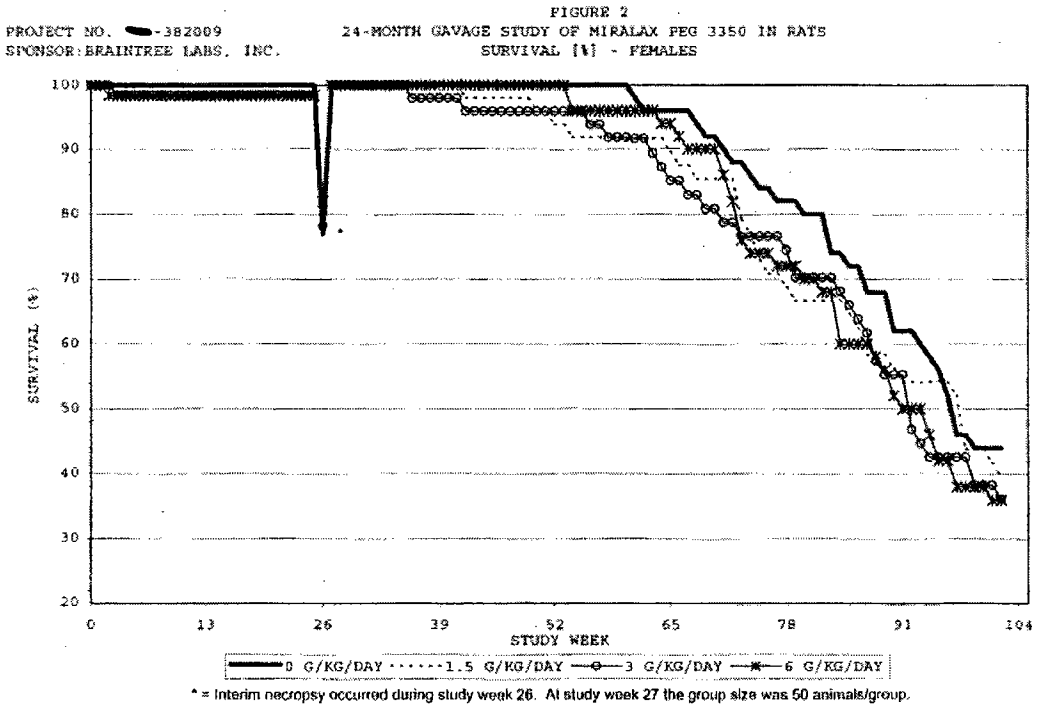
The survival curves (from page 80 and 81 of study report) are shown below.

Appears This Way
On Original

FIGURE 1
PROJECT NO. [redacted]-382009 24-MONTH GAVAGE STUDY OF MIRALAX PEG 3350 IN RATS
SPONSOR:BRAINTREE LABS, INC. SURVIVAL [%] - MALES



* = Interim necropsy occurred during study week 26. At study week 27 the group size was 50 animals/group.



Clinical signs: Treatment-related clinical signs included soft feces and brown material (wet and/or dry) on the urogenital and/or anogenital areas at 3 and 6 g/kg/day groups in males and at 1.5, 3 and 6 g/kg/day groups in females. These findings were more prevalent in the males than females.

Palpable mass: There were no treatment-related effects.

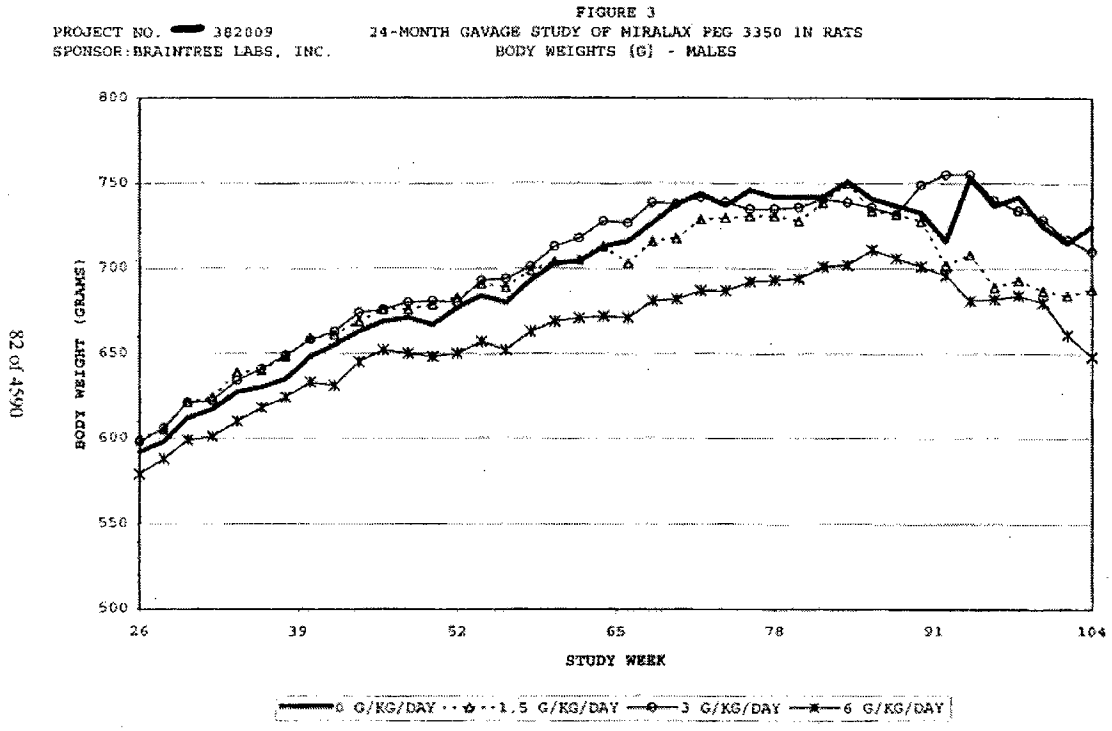
Body weights: The mean initial (26-week) and final (104-week) body weight of control males was 592 and 725 g, respectively. The mean initial (26-week) and final (103-week) body weight of control females was 331 and 446 g, respectively. There appeared to be a decrease in body weight (5-6%) at the end of the study in males at 1.5 and 6 g/kg/day compared to control. In females, body weight was reduced by 4% at week 3 at high dose. The following table shows the body weight data.

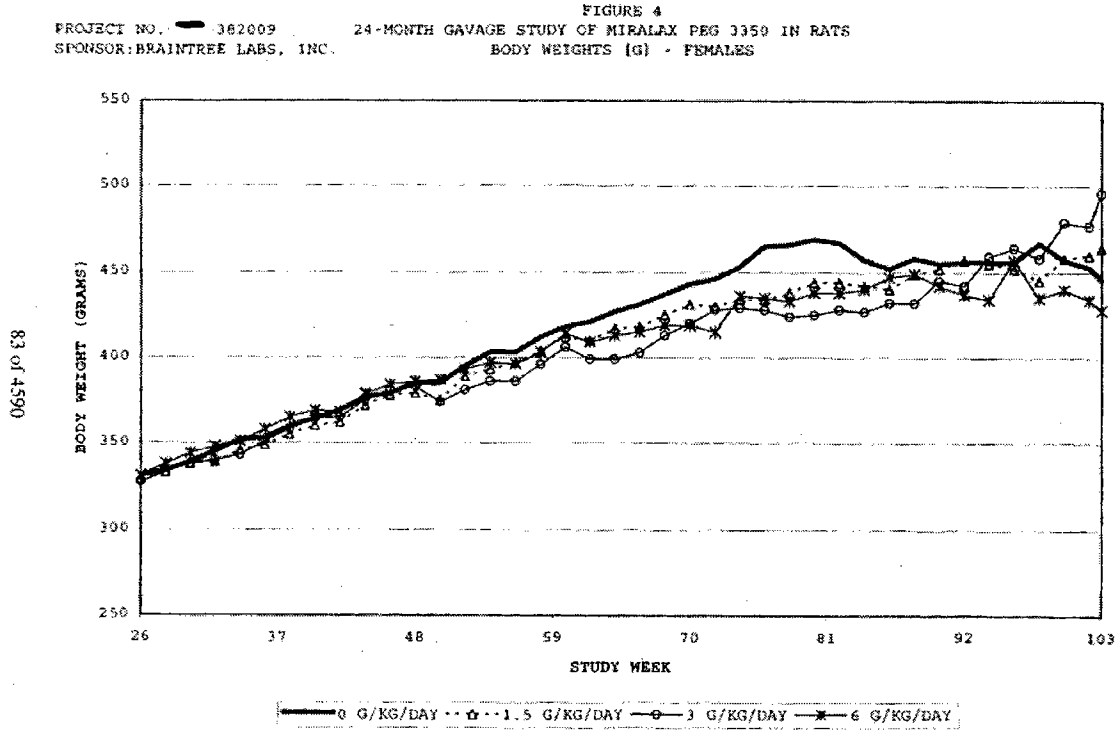
Week	Males (Dose: g/kg/day)					Females (Dose: g/kg/day)				
	0	1.5	3	6		0	1.5	3	6	
26	592	600	598	579		331	329	327	331	
38	635	648	649	649		360	355	358	365	
50	667	679	681	648		385	375	374	387	
62	704	705	718	671		421	410	399	409	

74	737	730	739	687*		453	434	429	436	
86	741	734	736	711		452	440	432	447	
98	742	693	734	684		467	445	458	435	
100	725	687	729	680		457	458	479	440	
103						446	464	496	428	
104	725	688	710	648						
Body Weight (% of Control)										
Final Week	100	95	100	94		100	104	107	96	

*: Statistically significant from the control

The body weight curves are shown below (from page 82 and 83 of the study report).





Food consumption: The mean initial and final food consumption in control males was 24 and 26 g/animal/day, respectively. The mean initial and final food consumption in control females was 19 and 21 g/animal/day, respectively. There were no significant treatment-related effects on food consumption.

Hematology and Clinical Chemistry: There were no significant treatment-related changes.

Ophthalmoscopy: There were no treatment-related ocular findings.

Gross pathology: Treatment-related changes were observed at 6 g/kg/day in the cecum for males and females. An increase in incidence of distended cecum was observed in animals that died or were euthanized *in extremis*. This observation was not noted in the animals at the scheduled necropsy.

Histopathology:

Non-neoplastic: Treatment-related histopathological changes were observed in the kidney (chronic progressive nephropathy, vacuolation, hyperplasia of clear cell and tubule cell), urinary bladder (cytoplasmic vacuolation of the superficial transitional cell

layer), colon (glandular atrophy associated with dilatation), adrenal medulla (hyperplasia) and liver (basophilic and clear cell foci). The following tables (from page 58, 61, 62, 63 and 64 of the study report) show the histopathologic changes in the above-mentioned organs.

Text Table 6: Incidence of Renal Changes in Females

	Control		1.5 g/kg		3 g/kg		6 g/kg	
Number examined	PD	PN	PD	PN	PD	PN	PD	PN
	27	22	28	19	27	15	24	18
Chronic progressive nephropathy	8	14	11	5	11	9	6	9
Vacuolation	2	0	**9**	**5**	**14**	**7**	**19**	**15**
Minimal	1	0	6	5	9	6	4	11
Mild	1	0	3	0	2	1	8	4
Moderate	0	0	0	0	1	0	3	0
Severe	0	0	0	0	2	0	4	0
Hyperplasia (clear cell)	0	0	**7**	**7**	**12**	**7**	**17**	**13**
Minimal	0	0	6	7	9	6	8	10
Mild	0	0	1	0	3	1	9	3
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Hyperplasia (tubular)	0	9	4	10	6	**11**	5	**13**
Minimal	0	8	4	10	5	6	4	10
Mild	0	0	0	0	1	5	1	2
Moderate	0	0	0	0	0	0	0	1
Severe	0	1	0	0	0	0	0	0

PD: premature death
PN: primary necropsy

Text Table 7: Incidence of Vacuolation in the Urinary Bladder

	Control		1.5 g/kg/day		3 g/kg/day		6 g/kg/day	
	PD	PN	PD	PN	PD	PN	PD	PN
Males	0/27	0/20	1/28	0/19	1/19	**14/24**	**9/23**	**23/25**
Females	0/27	1/22	0/31	0/19	2/31	**2/15**	**12/28**	**16/18**

PD: premature death
PN: primary necropsy

Text Table 8: Combined Incidence of Glandular Atrophy in the Colon in Males

	Control	1.5 g/kg/day	3 g/kg/day	6 g/kg/day
Number examined[a]	43	41	40	42
Glandular Atrophy	2	8	7	10
Minimal	2	8	7	8
Mild	0	0	0	2

[a] = Excludes tissues too autolyzed to examine.

Text Table 9: Combined Incidence of Glandular Atrophy in the Colon in Females

	Control	1.5 g/kg/day	3 g/kg/day	6 g/kg/day
Number examined[a]	48	49	43	45
Glandular Atrophy	11	13	7	16
Minimal	11	13	7	16

[a] = Excludes tissues too autolyzed to examine.

Text Table 10: Combined Incidence of Adrenal Medulla Hyperplasia in Males

	Control	1.5 g/kg/day	3 g/kg/day	6 g/kg/day
Number examined[a]	46	49	48	47
Adrenal medulla hyperplasia	9	20	16	20
Minimal	4	9	8	7
Mild	2	6	6	7
Moderate	1	5	1	5
Severe	2	0	1	1

[a] = Excludes tissues too autolyzed to examine.

Text Table 11: Combined Incidence of Basophilic and Clear Cell Foci in the Liver of Males (50 males/group)[a]

Foci	Control	1.5 g/kg/day	3 g/kg/day	6 g/kg/day
Basophilic cell	8	11	6	15
Minimal	5	4	3	10
Mild	3	7	3	3
Moderate	0	0	0	1
Severe	0	0	0	1
Clear cell	6	4	10	13
Minimal	2	1	2	5
Mild	3	3	6	6
Moderate	1	0	2	2

[a] = Excludes tissues too autolyzed to examine

Neoplastic: No test article-related increased neoplasms were observed at any dose level of Miralax PEG 3350. There were no statistically significant increases in any tumors when compared to the control group. One female at 3 g/kg/day group had a renal tubular adenoma. This was not considered test article-related in the absence of a dose response. The following summary tables (from pages 14-23 of the study report) show the tumor findings.

-382009 MiraLax™ PEG-3350
Braintree Laboratories, Inc.

SUMMARY TABLE

Carcinogenicity — **Study Title:** A 24-Month Oral (Gavage) Combined Chronic Toxicity/Carcinogenicity Study Of MiraLax™ PEG-3350 In Rats — Page 1

Species/Strain: ■ .CD®(SD)IGS BR Rats — **Duration of Dosing:** 98 weeks (3 and 6 g/kg/day females), 103 weeks (0 and 1.5 g/kg/day females), 104 weeks (males) — **Test Article:** MiraLax™ PEG-3350 — **Study No.** ■ -382009

Initial Age: 7 weeks — **Method of Administration:** Oral Gavage

Date of First Dose: July 9, 2002 — **Vehicle/Formulation:** Deionized Water — **GLP Compliance:** Yes

Treatment of Controls: Deionized Water

Basis for High-Dose Selection: Results of previous toxicology studies.

Special Features: Chronic Phase - Up to fifteen rats/sex/group scheduled for euthanasia at study week 26 for the chronic phase. Renal function was evaluated for all animals euthanized during study week 26. An additional 11 animals/group/sex treated with MiraLax™ PEG-3350 at 1.5, 3 and 6 g/kg/day were used for toxicokinetic analysis: samples were taken from 3 animals/sex at 0, 1, 2, 6, 12 and 24 hours after dose administration during study week 26 (equivalent to 27 weeks of treatment). Carcinogenicity Phase - Dose administration in the 3 and 6 g/kg/day female groups was discontinued during study week 98, when the survival reached the protocol-specified survival of 20 animals within any group. All the surviving females in each group where then euthanized during study week 103, when the protocol-specified survival of 15 animals was reached in the 3 g/kg/day female group. The discontinuation of dosing during study week 98 for the 3 and 6 g/kg/day female groups or the early termination during study week 103 for all surviving females animals in each group was not attributed to the test article as survival was similar in the control group.

Daily Dose (g/kg/day)	0 (Control)		1.5		3		6	
Gender	M	F	M	F	M	F	M	F
Number of Animals								
At Start	65	65	65	65	65	65	65	65
6-Month Chronic Euthanasia (Week 26)	12	15	12	14	12	13	12	10
Died/Euthanized or Moribund[a]	32	28	34	30	28	33	26	33
Accidental Deaths	1	0	0	2	1	4	2	4
Terminal Euthanasia (Week 103, females)	NA	22	NA	19	NA	15	NA	18
Terminal Euthanasia (Week 104, males)	20	NA	19	NA	24	NA	25	NA
Survival[b]								
Ratio (alive/no. in group)	20/50	22/50	19/50	19/48	24/49	15/47	25/49	18/50
Percentage	40%	44%	38%	40%	49%	32%	51%	36%

NA = Not Applicable
a = Does not include accidental deaths
b = Percent survival based on number of animals surviving through the last full week prior to necropsy. Accidental deaths were excluded from survival calculations.

-382009 MiraLax™ PEG-3350

Braintree Laboratories, Inc.

SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. -382009 (continued)										Page 2
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Body Weight (%[c])											
At 6 Months	592 g	331 g	↑1.4	↓0.6	↑1.0	↓1.2	↓2.2	0.0			
End of Study	725 g	446 g	↓5.1	↑4.0	↓2.1	↑11.2	↓10.6	↓4.0			
Food Consumption (%[c])											
At 6 Months	25 g/day	19 g/day	↑4.0**	0.0	↑4.0	0.0	↑4.0	0.0			
End of Study	26 g/day	21 g/day	0.0	0.0	0.0	↑9.5	↓3.8	↓4.8			
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Adipose tissue (no. examined)	NA	1	NA	1	NA	1	NA	1			
Hiberanoma, malignant	0	0	0	1	0	0	0	0			
Adrenal Cortex (no. examined)	48	49	47	49	48	49	47	49			
Adenoma	0	1	0	1	0	1	0	0			
Adrenal Medulla (no. examined)	46	50	49	49	48	48	47	50			
Pheochromocytoma, benign	2	0	5	0	5	0	5	1			
Pheochromocytoma, malignant	0	1	2	1	1	1	3	0			
Aorta (no. examined)	50	50	31	31	27	35	49	50			
Hibernoma, malignant	0	0	0	0	1	0	0	0			
Brain (no. examined)	50	50	31	31	26	35	50	50			
Astrocytoma, malignant	0	0	1	0	0	1	2	1			
Reticulosis, malignant	0	0	0	0	0	1	0	0			
Bulbourethral gland (no. examined)	NA	NA	NA	NA	NA	NA	1	NA			
Fibrosarcoma	0	0	0	0	0	0	1	0			

NA = not applicable Dunnett's test ** = p<0.01

c = For controls, group means are shown. For treated groups, percent differences from the control group are shown. Statistical significance is based on actual data (not on the percent differences)

d = The total number of animals in group does not include animals euthanized at study week 26.

[redacted]-382009
Braintree Laboratories, Inc.

MiraLax™ PEG-3350

SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted]-382009 (continued)										Page 3
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Cervix (no. examined)	NA	49	NA	33	NA	35	NA	50			
Papilloma, squamous cell	0	0	0	0	0	1	0	0			
Leiomyoma	0	0	0	1	0	0	0	0			
Polyp, endometrial, stromal	0	0	0	0	0	1	0	0			
Sarcoma, endometrial, stromal	0	0	0	1	0	0	0	0			
Clitoral gland (no. examined)	NA	45	NA	28	NA	32	NA	46			
Papilloma, squamous cell	0	0	0	1	0	0	0	1			
Ears (no. examined)	NA	1	NA	NA	NA	NA	NA	1			
Papilloma, squamous cell	0	1	0	0	0	0	0	1			
Femur (no. examined)	50	NA	30	NA	26	NA	50	NA			
Osteosarcoma	0	0	0	0	0	0	1	0			
Heart (no. examined)	NA	50	NA	33	NA	35	NA	50			
Schwannoma, endocardial, benign	0	1	0	0	0	0	0	0			
Ileum (no. examined)	NA	48	NA	29	NA	27	NA	43			
Leiomyoma	0	0	0	0	0	1	0	0			
Jejunum (no. examined)	NA	47	NA	27	NA	27	NA	42			
Leiomyoma	0	1	0	0	0	0	0	0			
Kidneys (no. examined)	44	49	44	47	41	42	48	42			
Liposarcoma	0	0	1	0	0	0	0	0			
Adenoma, renal tubule	0	0	0	0	0	1	0	0			
Lipoma	0	0	0	0	0	0	0	1			
Liver (no. examined)	50	50	50	50	50	50	50	50			
Adenoma, hepatocellular	0	0	2	0	0	0	1	0			
Carcinoma, hepatocellular	0	0	1	0	1	0	0	0			

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. [redacted] 382009 (continued)										Page 4
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Lungs (no. examined)	50	50	37	32	27	36	50	50			
Hibernoma, malignant	0	0	2	0	0	0	0	1			
Carcinoma, bronchiolo-alveolar	0	0	0	1	0	0	0	0			
Lymph node, axial (no. examined)	NA	NA	1	NA	1	NA	1	NA			
Lipoma	0	0	0	0	0	0	1	0			
Lymph node, mediastinal (no. examined)	NA	1	NA	1	NA	3	NA	2			
Liposarcoma	0	0	0	0	0	1	0	0			
Mammary gland (no. examined)	5	50	2	40	5	42	3	49			
Fibroadenoma	0	18	0	15	2	9	0	17			
Adenoma	0	3	0	3	1	3	0	2			
Adenocarcinoma	1	12	0	14	1	7	0	12			
Fibrosarcoma	0	2	0	0	0	0	0	0			
Carcinoma, undifferentiated	0	0	0	0	0	0	0	2			
Nasal level III (no. examined)	NA	50	NA	31	NA	33	1	49			
Carcinoma, squamous cell	0	1	0	0	0	0	0	0			
Oral cavity (no. examined)	NA	NA	NA	NA	NA	NA	1	NA			
Osteosarcoma	0	0	0	0	0	0	1	0			
Ovaries (no. examined)	NA	50	NA	38	NA	36	NA	48			
Sertoli cell tumor, benign	0	0	0	0	0	1	0	0			
Luteoma	0	1	0	0	0	0	0	0			
Mesothelioma, malignant	0	0	0	1	0	0	0	0			
Pancreas (no. examined)	46	50	29	31	27	34	49	48			
Adenoma, islet cell	4	2	0	0	2	0	7	0			
Carcinoma, acinar cell	0	0	0	1	0	0	0	0			
Parathyroid (no. examined)	45	NA	21	NA	22	NA	42	NA			
Adenoma	1	0	0	0	0	0	0	0			

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. 382009 (continued)										Page 5
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Pituitary (no. examined)	50	50	42	46	35	47	47	50			
Adenoma, pars distalis	27	40	28	34	27	36	22	36			
Seminal vesicles (no. examined)	47	NA	29	NA	19	NA	49	NA			
Carcinoma, undifferentiated	0	0	1	0	0	0	0	0			
Skin (no. examined)	50	49	35	34	35	35	50	48			
Basal cell tumor, benign	1	0	0	1	1	0	2	0			
Basal cell tumor, malignant	0	0	0	0	0	0	0	1			
Fibroma	1	0	1	0	5	0	1	0			
Lipoma	2	0	0	1	2	0	0	1			
Papilloma, squamous cell	0	0	0	0	0	0	1	0			
Keratoacanthoma	0	0	2	0	1	0	0	0			
Schwannoma, malignant	0	0	0	0	0	0	0	1			
Soft tissue - thorax (no. examined)	2	1	1	NA	NA	NA	3	NA			
Hibernoma, malignant	2	1	1	0	0	0	1	0			
Hibernoma	0	0	0	0	0	0	1	0			
Stomach, non (no. examined)	50	49	30	31	26	35	50	50			
Papilloma, squamous cell	1	0	0	0	0	0	0	0			
Systemic tumors (no. examined)	2	3	3	1	3	3	2	4			
Lymphoma, malignant	1	0	0	0	2[e]	0	0	1			
Sarcoma, histiocytic	1	1	3	0	2	0	2	0			
Leukemia, granulocytic	0	2	0	1	0	2	1	3			
Hemangiosarcoma	0	0	0	0	0	1	0	0			
Tail (no. examined)	29	NA	29	NA	23	NA	19	NA			
Keratoacanthoma, benign	0	0	0	0	0	0	1	0			
Papilloma, squamous cell	0	0	0	0	1	0	0	0			

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.
e = Includes male no. 5022 euthanized *in extremis* at study week 14.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. 382009 (continued)										Page 6
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Testes (no. examined)	50	NA	33	NA	29	NA	50	NA			
Adenoma, interstitial cell	2	0	0	0	1	0	2	0			
Thyroid glands (no. examined)	45	48	26	30	25	30	44	44			
Adenoma, c-cell	4	2	3	2	6	1	2	4			
Adenoma, follicular cell	0	2	0	1	2	0	0	0			
Carcinoma, c-cell	1	0	0	0	0	2	2	0			
Carcinoma, follicular cell	0	0	0	1	0	0	0	0			
Thymus (no. examined)	48	50	29	30	25	33	49	49			
Fibrosarcoma	1	0	0	0	0	0	0	0			
Hibernoma, malignant	0	0	0	0	0	1	0	1			
Liposarcoma	0	0	0	1	0	0	0	0			
Thyoma, benign	0	0	0	0	0	1	0	0			
Urinary bladder (no. examined)	47	49	47	50	43	46	48	46			
Leiomyoma	1	0	0	0	0	0	0	0			
Uterus (no. examined)	NA	49	NA	37	NA	39	NA	49			
Polyp, endometrial stromal	0	3	0	4	0	0	0	4			
Carcinoma	0	0	0	0	0	2	0	1			
Schwannoma, malignant	0	1	0	0	0	0	0	0			
Adenoma, endometrial	0	0	0	0	0	1	0	0			
Vagina (no. examined)	NA	49	NA	31	NA	34	NA	48			
Leiomyoma	0	0	0	0	0	0	0	1			

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. 382009 (continued)										Page 7
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Gender	M	F	M	F	M	F	M	F			
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Metastatic sites:											
Adrenal Cortex (no. examined)	48	49	47	49	48	49	47	49			
Osteosarcoma; femur	0	0	0	0	0	0	1	0			
Aorta (no. examined)	NA	50	NA	31	NA	35	NA	50			
Carcinoma; uterus	0	0	0	0	0	1	0	0			
Brain (no. examined)	50	50	31	31	26	35	50	50			
Osteosarcoma; femur	0	0	0	0	0	0	1	0			
Cecum (no. examined)	NA	49	NA	27	NA	29	NA	44			
Carcinoma, uterus	0	0	0	0	0	0	0	1			
Cervix (no. examined)	NA	49	NA	33	NA	35	NA	50			
Carcinoma, uterus	0	0	0	0	0	0	0	1			
Diaphragm (no. examined)	NA	NA	NA	NA	NA	1	NA	1			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Harderian glands (no. examined)	NA	50	NA	34	NA	35	NA	50			
Carcinoma, squamous cell; nasal cavity	0	1	0	0	0	0	0	0			
Ileum (no. examined)	NA	48	NA	29	NA	27	NA	43			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Kidneys (no. examined)	44	49	44	47	41	42	48	42			
Osteosarcoma; femur	0	0	0	0	0	0	1	0			
Hibernoma, malignant; thymus	0	0	0	0	0	0	0	1			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Liver (no. examined)	50	50	50	50	50	50	50	50			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Hibernoma, malignant; thymus	0	0	0	0	0	0	0	1			

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No.		-382009 (continued)						Page 8
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6		
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50
Animals with Neoplastic Findings:								
Metastatic sites (continued):								
Lungs (no. examined)	50	50	37	32	27	36	50	50
Carcinoma, uterus	0	0	0	0	0	1	0	0
Hibernoma, malignant; thoracic soft tissue	2	0	1	0	0	0	0	0
Hibernoma, malignant; thymus	0	0	0	0	0	0	0	1
Pheochromocytoma, malignant; adrenal medulla	0	1	0	0	0	0	0	0
Osteosarcoma; femur	0	0	0	0	0	0	1	0
Hibernoma, malignant; lung	0	0	1	0	0	0	0	0
Lymph node, man (no. examined)	NA	50	NA	31	NA	37	NA	50
Carcinoma, squamous cell; nasal cavity	0	1	0	0	0	0	0	0
Lymph node, mediastinal (no. examined)	NA	1	NA	1	NA	3	NA	2
Carcinoma, uterus	0	0	0	0	0	1	0	1
Lymph node, mesenteric (no. examined)	NA	50	NA	31	NA	34	NA	50
Carcinoma, uterus	0	0	0	0	0	1	0	1
Lymph node, ren (no. examined)	3	NA	3	NA	1	NA	1	NA
Pheochromocytoma, malignant; adrenal medulla	0	0	1	0	0	0	0	0
Marrow, sternum (no. examined)	NA	50	NA	31	NA	35	NA	49
Hibernoma, malignant; thymus	0	0	0	0	0	0	0	1
Ovaries (no. examined)	NA	50	NA	38	NA	36	NA	48
Carcinoma, uterus	0	0	0	0	0	0	0	1

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.

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SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. -382009 (continued)										Page 9
Daily Dose (g/kg/day)	0 (Control)		1.5		3		6				
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50			
Animals with Neoplastic Findings:											
Metastatic sites (continued):											
Pancreas (no. examined)	46	50	29	31	27	34	49	48			
Carcinoma, islet cell	1	0	0	0	0	0	1	0			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Rectum (no. examined)	45	NA	24	NA	17	NA	45	NA			
Leiomysarcoma	1	0	0	0	0	0	0	0			
Skeletal muscle (no. examined)	50	50	30	31	26	35	50	49			
Osteosarcoma; femur	0	0	0	0	0	0	1	0			
Carcinoma, uterus	0	0	0	0	0	0	0	1			
Skin (no. examined)	50	49	35	34	35	35	50	48			
Carcinoma, squamous cell; nasal cavity	0	1	0	0	0	0	0	0			
Soft tissue - abdomen (no. examined)	NA	1	1	1	1	1	NA	NA			
Carcinoma, bronchiolo-alveolar	0	0	0	1	0	0	0	0			
Carcinoma, uterus	0	0	0	0	0	1	0	0			
Soft tissue - thorax (no. examined)	2	NA	1	NA	NA	NA	3	NA			
Osteosarcoma; femur	0	0	0	0	0	0	1	0			
Spleen (no. examined)	NA	50	NA	31	NA	36	NA	50			
Hibernoma, malignant; thymus	0	0	0	0	0	0	0	1			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Stomach, glandular (no. examined)	NA	49	NA	31	NA	35	NA	45			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Stomach, non-glandular (no. examined)	NA	49	NA	31	NA	35	NA	50			
Carcinoma, uterus	0	0	0	0	0	1	0	1			
Thymus (no. examined)	48	50	29	30	25	33	49	49			
Osteosarcoma; femur	0	0	0	0	0	0	1	0			
Carcinoma, uterus	0	0	0	0	0	1	0	0			

NA = not applicable
d = The total number of animals in group does not include animals euthanized at study week 26.

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Braintree Laboratories, Inc.

SUMMARY TABLE (CONTINUED)

Carcinogenicity	Study No. L-382009 (continued)								Page 10
Daily Dose (mg/kg/day)	0 (Control)		1.5		3		6		
Total Number of Animals in Group[d]	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	
Animals with Neoplastic Findings:									
Metastatic sites (continued):									
Thyroid glands (no. examined)	45	48	26	30	25	30	44	44	
Carcinoma, c-cell	1	0	0	0	0	0	2	0	
Urinary bladder (no. examined)	NA	49	NA	50	NA	46	NA	46	
Carcinoma, uterus	0	0	0	0	0	0	0	1	
Noteworthy Findings:									
Gross Pathology:									
Cecum (no. examined)	33	28	34	32	29	37	28	37	
Distended	1	0	2	2	3	1	8	4	
Histopathology (non-neoplastic findings):									
Adrenal Medulla (no. examined)	46	50	49	49	48	48	47	50	
Hyperplasia	9	8	20	9	16	15	20	12	
Colon (no. examined)	43	48	41	49	40	43	42	45	
Glandular atrophy	2	11	8	13	7	7	10	16	
Kidneys (no. examined)	44	49	44	47	41	42	48	42	
Clear cell hyperplasia	1	0	18	14	33	19	40	30	
Tubular epithelium vacuolation	1	2	22	14	30	21	42	34	
Tubular hyperplasia	11	9	14	14	18	17	25	18	
Liver (no. examined)	50	50	50	50	50	50	50	50	
Hepatocellular vacuolation	3	6	11	5	9	6	15	8	
Clear cell foci	6	7	4	4	10	3	13	3	
Basophilic cell foci	8	23	11	17	6	12	15	16	
Urinary Bladder (no. examined)	47	49	47	50	43	46	48	46	
Cytoplasmic vacuolation	0	1	1	0	15	4	32	28	

NA = not applicable

d = The total number of animals in group does not include animals euthanized at study week 26.

Toxicokinetics: None

Summary: In a 104-week oral (gavage) carcinogenicity study in SD rats, animals (n = 50/sex/group) were treated with Miralax PEG 3350 at 0 (water), 1.5, 3 and 6 g/kg/day (10 ml/kg). There was no significant impact on overall survival. Clinical signs included increased incidences of soft feces and brown material (dry and/or wet) on the urogenital and/or anogenital areas at 3 and 6 g/kg/day group males and the 1.5, 3 and 6 g/kg/day group females. Treatment-related histopathological changes were observed in the kidney (chronic progressive nephropathy, vacuolation, hyperplasia of clear cell and tubule cell), urinary bladder (cytoplasmic vacuolation, of the superficial transitional cell layer), colon (glandular atrophy associated with dilatation), adrenal medulla (hyperplasia) and liver (basophilic and clear cell foci). There were no treatment-related tumor findings in any tissue that was attributed to treatment with Miralax PEG 3500. Overall, the results appeared to be negative for any tumor findings.

2.6.6.6 Reproductive and developmental toxicology

Fertility and Early Embryonic Development

Study title: Fertility and Early Embryonic Development to Implantation (Segment I) with Miralax PEG 3350 in Rats

Key study findings: In a Segment I study in rats, males and females were treated at 0, 0.5, 1.0 and 2.0 g/kg/day. Male and female survival was unaffected by test article administration in all dose groups. No treatment-related effects were observed on mean body weights, food consumption and organ weights at any of the tested doses. No test article-related effects were observed on male or female reproductive parameters (estrous cycles, mating and fertility indices) or on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate, sperm motility and sperm morphology). Intrauterine survival (pre- and post-implantation losses, viable embryos and numbers of corpora lutea and implantation sites) was unaffected by test article administration at all dose levels.

Study no.: [redacted] 382015
Volume #, and page #: 13.1-13.2, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: September 13, 2002
GLP compliance: A statement of compliance was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Miralax PEG 3350, Lot No. 1275, [redacted]

Methods:

Doses: 0 (water), 0.5, 1 and 2 g/kg/day
Species/strain: Rat/Sprague Dawley
Number/sex/group: 25/sex/group
Route, formulation, and volume: Oral, solution and 5 ml/kg
Satellite groups used for toxicokinetics: None
Study design: Males received a minimum of 28 daily doses prior to mating and throughout the mating period through one day prior to euthanasia. Females received a minimum of 14 daily doses prior to pairing and were treated through gestation day 7 (GD 7). The following table (from page 17 of the study report) shows the study design. The basis of dose selection was not mentioned.

Group Number	Test Article	Dosage Level (g/kg/day)	Dosage Concentration (g/mL)	Dosage Volume (mL/kg)	Number of Animals Males	Females
1	Vehicle Control	0	0	5	25	25
2	MiraLax®(PEG-3350)	0.5	0.1	5	25	25
3	MiraLax®(PEG-3350)	1	0.2	5	25	25
4	MiraLax®(PEG-3350)	2	0.4	5	25	25

Parameters and endpoints evaluated: All rats were observed twice daily for mortality and clinical signs. Body weights were recorded on a weekly basis. Food consumption was measured twice weekly. Vaginal lavages were performed daily and the slides were evaluated to determine the stage of estrous. Mating and fertility indexes were calculated. On GD 15, the following parameters were evaluated: the number of corpora lutea, early resorptions and total number of implantations, and viability of the embryos. The following spermatogenic endpoints were evaluated: sperm motility, sperm morphology, and sperm count, etc.

Results:

Mortality and clinical signs: All males survived to the scheduled necropsy. Soft stool was noted at increased incidences in all test article-treated groups when compared to the control group. Female no. 11628 in the control group was euthanized on study day 49 due to presumed pregnancy. No clinical findings were noted for this female prior to euthanasia. In addition, female no. 11671 in the 1 g/kg/day group was euthanized on study day 52 due to unexpected delivery. Clinical findings noted for this animal prior to euthanasia included hair loss and red material around the nose.

Body weight: The mean initial and final weights of the control males were 286 and 488 g, respectively. The mean initial and final weights of the control females were 208 and 245 g, respectively. There were no significant treatment-related effects in either sex.

Food consumption: The mean initial and food consumption in control males were 24 and 26 g/animal/day, respectively. The mean initial and final food consumption in control females were 18 and 20 g/animal/day, respectively. There were no significant treatment-related changes in either sex.
Toxicokinetics: None

Necropsy: At the scheduled necropsy, no test article-related macroscopic findings were observed at any dose level. One female each in the control and 1 g/kg/day groups had no evidence of mating and was gravid. One, three and one females in the control, 0.5 and 2 g/kg/day groups, respectively, were nongravid. Female no. 11628 (no evidence of mating) in the control group had 13 fetuses with no apparent malformations *in utero*. Female no. 11671 (no evidence of mating) in the 1 g/kg/day group delivered three pups (two live pups, one dead pup) with no apparent external malformations on study day 52.

Fertility parameters: There were no test article-related effects on male reproductive performance at any of the tested doses. In addition, spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate, sperm motility and sperm morphology) were also unaffected by test article administration at all dose levels.

Intrauterine parameters (pre- and post-implantation losses, viable embryos and numbers of corpora lutea and implantation sites) were unaffected by test article administration at all dose levels. However, an increase (not statistically significant) in the mean litter proportion of pre-implantation loss was noted at 2 g/kg/day group (15.3% per litter) compared to the control group (8.2 % per litter). Because this value was within the historical control data range (4.0-15.7%), this increase was not attributed to the test article. The following table shows the male and female fertility parameters.

PARAMETER	DOSE (G/KG/DAY)			
	0	0.5	1.0	2.0
FEMALE				
N=	25	25	25	25
Mating Index, % (female)	100 (25/25)	100 (25/25)	100 (25/25)	100 (25/25)
Pregnant Dams	23	22	24	24
Fertility Index, % (female)	96 (24/25)	88 (22/25)	100 (25/25)	96 (24/25)
Corpora lutea/dam	15.9 (365/23)	16.7 (367/22)	16.1 (387/24)	15.5 (373/24)
Implant sites/dam	13 (285/22)	12.4 (272/22)	12.1 (290/24)	12.4 (286/23)
Implantation sites, mean	14.5	15.6	14.8	13.5
Pre-implantation loss, mean	1.4	1.0	1.4	2.0
Post-implantation loss, mean	0.6	0.8	0.6	0.7
Resorptions - Total - early - late	 0.6 0.6 0.0	 0.8 0.8 0.0	 0.6 0.6 0.0	 0.7 0.7 0.0
Live fetuses/dam	13.9	14.9	14.2	12.8
Dead fetuses/dam	0	0	0	0
MALE				
Mating Index, %	96	100	96	96
Fertility Index, %	92	88	96	92
Sperm motility, %	86	86	86	85
Sperm production rate (millions/g/day)	16.3	16.6	16.2	15.8
Sperm morphology, normal	99.8	99.8	99.8	99.7

Summary: In a Segment I study in rats, males and females were treated at 0, 0.5, 1.0 and 2.0 g/kg/day. Male and female survival was unaffected by test article administration in all dose groups. No treatment-related effects were observed on mean body weights, food consumption and organ weights at any of the tested doses. No test article-related effects were observed on male or female reproductive parameters (estrous cycles, mating and fertility indices) or on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate, sperm motility and sperm morphology). Intrauterine

survival (pre- and post-implantation losses, viable embryos and numbers of corpora lutea and implantation sites) was unaffected by test article administration at all dose levels.

Embryofetal Development

Study title: Embryofetal Development (Segment II) in Rats

Key study findings: In a Segment II study in rats, mated females were treated orally (gavage) with PEG 3350 at 0.5, 1 and 2 g/kg/day (5 ml/kg). No test article-related effects were observed at any dose level on survival, body weights, and food consumption. There were no significant treatment-related effects on any intrauterine parameters or C-section parameters. No significant treatment-related effects were observed on fetal external, visceral or skeletal parameters at any dose level. PEG 3350 did not appear to be teratogenic in this study.

Study no.: [redacted] 382013
Volume #, and page #: 14.1-14.2, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: August 7, 2002
GLP compliance: A statement of compliance was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Miralax PEG 3350, Lot No. 1275, [redacted]

Methods:

Doses: 0.5, 1 and 2 g/kg/day. The doses were selected based on the results of the previous Segment I study in rats.

Species/strain: Rat/Sprague Dawley

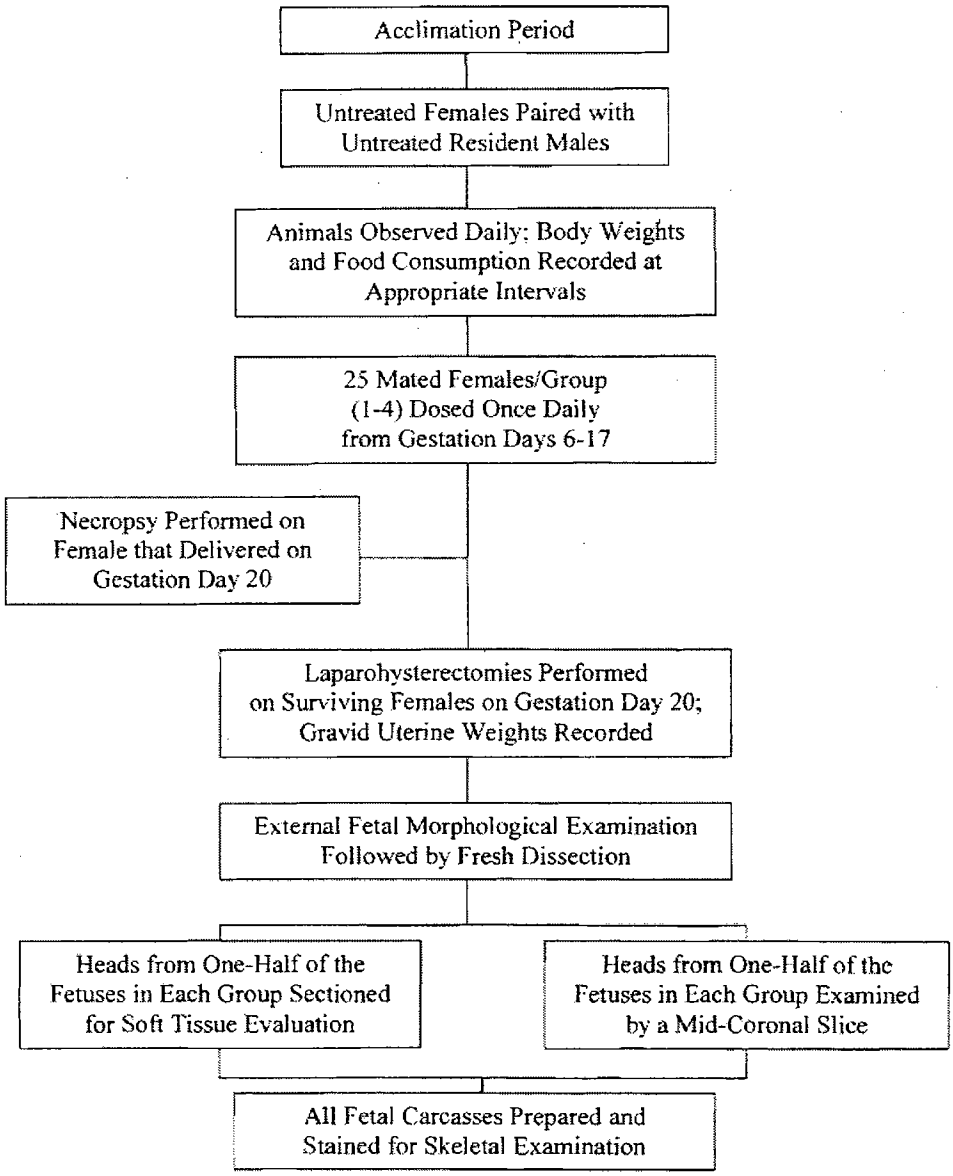
Number/sex/group: 25 mated females/dose

Route, formulation, and volume: Oral, solution, 5 ml/kg

Satellite groups used for toxicokinetics: A toxicokinetic phase was conducted in conjunction with the main study and involved six additional females/group, which were treated with PEG 3350 at 0.5, 1 and 2 g/kg/day on GD 6 through GD 17. On GD 17, blood samples for determination of plasma drug concentration were collected from the first three animals per group prior to dosing and at approximately 2 and 8 hours post-dosing and from the remaining three rats per group at 1, 4 and 24 hours post-dosing.

Study design: The study design is shown below (from page 11 of the study report).

3. STUDY DESIGN



Parameters and endpoints evaluated: All rats were observed twice daily for moribundity and mortality. Maternal body weights were recorded on GD 0, 6-18

(daily) and 20. Maternal food consumption was recorded on GD 0, 6-18 (daily) and 20. All maternal rats were euthanized on GD 20. The following ovary/uterine parameters were examined: number of corpora lutea, early and late resorptions and the total number of implantations. The fetuses were examined for external, visceral and skeletal anomalies.

Results:

Mortality (dams): None

Clinical signs (dams): None

Body weight (dams): The mean initial and final body weight of control females were 250 and 391 g, respectively. There were no treatment-related effects.

Food consumption (dams): The mean initial and final food consumption in control females were 22 and 23 g/animal/day, respectively. There were no treatment-related effects.

Toxicokinetics: The systemic exposures ($AUC_{0\text{-}24h}$) increased more than dose proportionately with dose from 0.5 to 2 g/kg/day. The t_{max} was 1 hour post-dosing. The following table (from page 25 of the study report) shows the TK data.

PEG-3350 (g/kg/day)	$AUC_{0\text{-}24h}$ (ng·h/mL) GD 17	C_{max} (ng/mL) GD 17	t_{max} (h) GD 17
0.5	794	490	1
1	4766	2084	1
2	12277	4546	1

Terminal and necroscopic evaluations: C-section data: Intrauterine growth and survival (post-implantation loss, live litter size and fetal body weight) were not significantly affected by treatment with PEG 3350 at all dose levels. Mean numbers of corpora lutea and implantation sites were similar across all groups, including the control, with the following exception. The mean number of corpora lutea at 2 g/kg/day group (15.9) was significantly lower than the control group value (17.8). The C-section data is shown below.

PARAMETER	DOSE (G/KG/DAY)			
	0	0.5	1.0	2.0
Pregnant Dams	25	24	20	25
Corpora lutea/dam	17.8 (445/25)	16.9 (405/24)	16.9 (338/20)	15.9* (397/25)
Implant sites/dam	15.3 (383/25)	15.2 (365/24)	15.0 (299/20)	15.0 (376/25)
Pre-implantation loss, mean	2.5	1.7	1.9	0.8
Post-implantation loss, mean	1.1	0.6	1.0	1.0

Resorptions (mean)				
- Total	1.0	0.6	1.0	1.0
- early	1.0	0.6	1.0	1.0
- late	0.0	0.0	0.0	0.0
Live fetuses/dam	14.2	14.6	14.0	14.0
Dead fetuses/dam	0	0	0	0
Fetal weight (g, mean)	3.6	3.7	3.7	3.7

*: Significantly different from control

Offspring (malformations, variations, etc.): There were no fetal external malformations or aberrations at any dose level.

Visceral malformations were noted in one fetus each in the control and 2 g/kg/day groups. Fetus nos. 95029-07 and 94962-07 in the control and 2 g/kg/day groups, respectively, had situs inversus (the trachea, esophagus, great and major vessels, heart, lungs, liver, stomach and/or spleen were laterally transposed). The finding in the 2 g/kg/day group was considered to be an isolated effect and not attributed to the test article.

Visceral variations in the test article-treated groups were limited to single findings of a major blood vessel variation [the right carotid and right subclavian arteries arose independently from the aortic arch (no brachiocephalic trunk)] and an accessory spleen in one fetus in each in the 1 and 2 g/kg/day groups, respectively. These soft tissue developmental variations were not attributed to the test article because they occurred only in single animals. In addition, single findings of a dark red adrenal gland and a dark red area on the liver were noted for fetus nos. 94987-05 (1 g/kg/day) and 95033-10 (2 g/kg/day), respectively. These findings were not classified as either malformations or developmental variations.

The only skeletal malformation noted in this study was a single occurrence of sternoschisis [sternal band nos. 3-6 (bilateral) were not joined] in the control group (fetus no. 94992-18). Skeletal developmental variations were observed across all dose groups, including the control group, and included cervical centrum no. 1 ossified, 14th rudimentary ribs, sternebrae nos. 5 and/or 6 unossified, hyoid unossified and 7th cervical ribs. These findings were not attributed to the test article in the absence of a dose-response and occurrences in the control animals.

Overall, there appears to be no significant treatment-related findings on fetal external, visceral and skeletal parameters. PEG 3350 did not appear to be teratogenic in this study.

The following table shows the fetal external, visceral and skeletal findings.

Parameter	0 g/kg/day	0.5 g/kg/day	1.0 g/kg/day	2.0 g/kg/day
Fetal External Observation				
Fetuses Examined Externally/litters	356/25	351/24	279/20	350/25
Fetal Visceral Malformation				
Fetuses/Litter Examined	356/25	351/24	279/20	350/25
Situs inversus	1	0	0	1
Fetal Visceral Variations				
Accessory spleen	0	0	0	1
Major blood vessel variation (no brachiocephalic trunk)	0	0	1	0
Fetal Skeletal Malformations				
Fetuses/Litter Examined	355/25	351/24	279/20	350/25
Sternoschisis	1	0	0	0
Fetal Skeletal Variations				
Sternebre malaligned	0	0	0	3
Cervical centrum # 1 ossified	110	89	62	112
7th Cervical Rib	4	3	1	5
4th Rudimentary ribs	21	22	26	37
Sternebre #5 and #6 unossified	8	15	4	4
Hyoid unossified	4	12	3	4
Reduced ossification of the 13th rib	2	2	1	0
Reduced ossification of the vertebral arches	0	0	1	0
25 Parasacral vertebrae	0	0	2	0

In a Segment II study in rats, mated females were treated orally (gavage) with PEG 3350 at 0.5, 1 and 2 g/kg/day. No test article-related effects were observed at any dose level on survival, body weights, and food consumption. There were no significant treatment-related effects on any intrauterine parameters or C-section parameters. No significant treatment-related effects were observed on fetal external, visceral or skeletal parameters at any dose level. PEG 3350 did not appear to be teratogenic in this study.

Study title: Embryofetal Development (Segment II) in Rabbits

Key study findings: In a Segment II study in New Zealand White rabbits, mated females were treated orally (gavage) with Miralax PEG 3350 at 0.5, 1 and 2 g/kg/day. There were no treatment-related mortalities. Treatment-related clinical findings included decreased defecation, soft stool and brown material on the tail at the high dose. In addition, decreased body weight gain and food consumption was observed at high dose during GD 7-21. There were no treatment-related effects on any intrauterine or C-section parameters. No significant treatment-related effects were observed on fetal external, visceral or skeletal parameters at any dose level. PEG 3350 did not appear to be teratogenic in this study.

Study no.: [redacted] 382014

Volume #, and page #: 16.1-16.2, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: August 7, 2002
GLP compliance: A statement of compliance was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Miralax PEG 3350, Lot No. 1275, [redacted]

Methods:

Doses: 0.5, 1 and 2 g/kg/day. The doses were selected based on the results of an oral (gavage) dose ranging study [redacted]-382007) in rabbits (GD 7 – GD 20, n = 6/dose) at 0.75 and 2 g/kg/day (5 ml/kg). In this study, one female at 2 g/kg/day aborted on GD 29. This animal showed decreased body weight gain and food consumption. There was no mortality. No treatment-related effects were observed on mean body weight, food consumption, gravid uterus weight at any dose level. There were no treatment-related effects on ay intrauterine growth or survival. There were no fetal external, visceral or skeletal malformations at any of the tested doses. Based on the results of this study, dose levels of 0.5, 1 and 2 g/kg/day as selected for the Segment II study in rabbits. The following table (from page 15 of the study report) shows the study group assignment.

Group Number	Test Article	Dosage Level (g/kg/day)	Concentration (g/mL)	Dose Volume (mL/kg)	Number of Animals
1	Vehicle	0	0	5	25
2	MiraLax® PEG-3350	0.5	0.1	5	25
3	MiraLax® PEG-3350	1	0.2	5	25
4	MiraLax® PEG-3350	2	0.4	5	25

Species/strain: Rabbit/New Zealand White

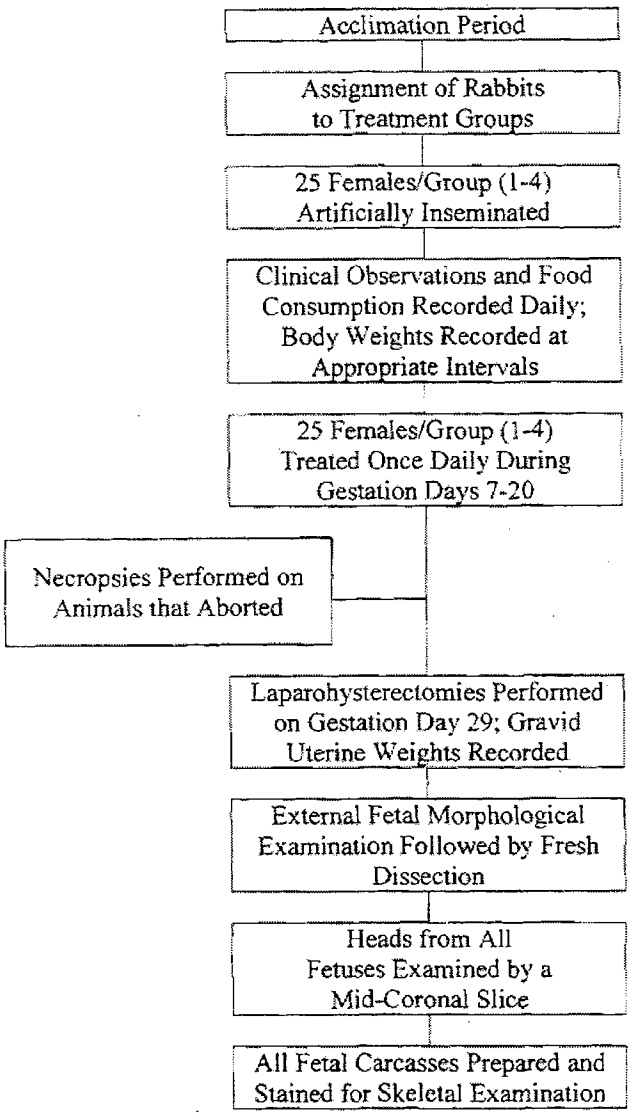
Number/sex/group: 25 mated females/dose

Route, formulation, and volume: Oral, solution, 5 ml/kg

Satellite groups used for toxicokinetics: A toxicokinetic phase was conducted in conjunction with the main study and involved three additional females/group, which were treated with PEG 3350 at 0.5, 1 and 2 g/kg/day on GD 6 through GD 17. On GD 20 blood samples were collected at 0, 1, 2, 4, 8 and 24 hours post-dose for TK analysis.

Study design: The study design is shown below (from page 12 of the study report).

3. **STUDY DESIGN**



Parameters and endpoints evaluated: All animals were observed twice daily for moribundity and mortality. Maternal body weights were recorded on GD 0, 7-21 (daily), 24 and 29. Maternal food consumption was recorded on GD 0-29. All maternal rabbits were euthanized on GD 29. The following ovary/uterine parameters were examined: number of corpora lutea, early and late resorptions and the total number of implantations. The fetuses were examined for external, visceral and skeletal findings.

Results:

Mortality (dams): None. One and two females in the 1 and 2 g/kg/day groups, respectively, aborted prior to the scheduled laparohysterectomy. Female no. 36992 (1 g/kg/day group) aborted one fetus, with no apparent malformations, on GD 24. Dried red material at the base of the tail and soft stool were noted at the time of abortion. Female no. 36957 (2 g/kg/day) aborted two fetuses (both partially cannibalized) on GD 23. Dried brown material at the base of the tail and red material on the cage bottom were noted at the time of abortion. Female no. 36989 (2 g/kg/day) aborted 12 fetuses (eleven with no apparent malformations and one partially cannibalized fetus) on GD 29. Red material on the cage bottom was noted at the time of abortion.

Clinical signs (dams): A higher incidence of decreased defecation was observed at 2 g/kg/day group during GD 13-23. Soft stool was observed at higher incidences at 0.5, 1 and 2 g/kg/day groups primarily through GD 24. Additionally, a higher incidence of wet or dried brown material at the base of the tail was observed in the 2 g/kg/day group during GD 0-29.

Body weight (dams): The mean initial and final body weight of control females were 3496 and 4129 g, respectively. Mean body weight gain at 2 g/kg/day was decreased (37% of control gain) during GD 7-21 when compared to control weight gain (205 g). There were no other significant treatment-related effects.

Food consumption (dams): The mean initial and final food consumption in control females were 217 and 152 g/animal/day, respectively. The food consumption was decreased (78% of control) at 2 g/kg/day when compared to control (200 g/animal/day) during GD 7-21.

Toxicokinetics: The systemic exposures ($AUC_{0\text{-}24h}$) increased more than dose proportionately with dose from 0.5 to 2 g/kg/day. The t_{max} was 1 hour. The following table (from page 29 of the study report) shows the TK data.

PEG-3350 (g/kg/day)	$AUC_{0\text{-}24h}$ (ng·h/mL) GD 20	C_{max} (ng/mL) GD 20	t_{max} (h) GD 20
0.5	624	317	1
1	2013	852	1
2	12042	1387	1

Terminal and necroscopic evaluations: C-section data: Intrauterine growth and survival (post-implantation loss, live litter size and fetal body weight) were not significantly affected by treatment with PEG 3350 at all dose levels. Mean numbers of corpora lutea and implantation sites were similar across all groups, including the control. The C-section data is shown below.

PARAMETER	DOSE (G/KG/DAY)			
	0	0.5	1.0	2.0
Pregnant Dams	22	23	22	17
Corpora lutea/dam	10.3 (226/22)	9.6 (220/23)	9.0 (198/22)	8.7 (148/17)
Implant sites/dam	7.2 (159/22)	6.5 (150/23)	6.8 (150/22)	5.6 (96/17)
Pre-implantation loss, mean	3.0	3.0	2.2	3.1
Post-implantation loss, mean	0.4	0.4	0.3	0.5
Resorptions (mean)				
- Total	0.3	0.4	0.3	0.4
- early	0.1	0.2	0.2	0.2
- late	0.2	0.2	0.1	0.2
Live fetuses/dam	6.9	6.1	6.5	5.2
Dead fetuses/dam	0	0	0	0
Fetal weight (g, mean)	45.7	45.7	45.8	46.9

Offspring (malformations, variations, etc.): There were no fetal external malformations or aberrations at any dose level.

Fetus no. 36994-05 in the 1 g/kg/day group had abnormal lobulation of the lungs (all lobes). This finding was not observed in the 2 g/kg/day and was not attributed to the test article. No other visceral malformations were observed.

Treatment-related visceral variations included major blood vessel variations [either the left carotid artery arose from the brachiocephalic trunk or the right carotid and right subclavian arteries arose independently from the aortic arch (no brachiocephalic trunk was present)], accessory spleen, retrocaval ureter and/or absent or small gallbladder. These soft tissue variations were not attributed to the test article in the absence of a dose-related response, occurred similarly in the control and test article-treated groups and/or were within the range of the [redacted] historical control data. However, the mean litter proportion of absent or small gallbladder was outside of the [redacted] historical control data (0.0% - 7.84%), three of the fetuses were from the same litter and had small gallbladders. The fourth occurrence was a single fetus with an absent gallbladder in another litter. Therefore, this finding was not attributed to the test article.

Skeletal malformations were observed in 4(3), 3(3), 3(3) and 0(0) fetuses (litters) in the control, 0.5, 1 and 2 g/kg/day groups, respectively. Vertebral anomalies with associated rib anomalies were observed in two, one and one fetuses in the control, 0.5 and 1 g/kg/day groups, respectively. These anomalies consisted of absent arches and/or halves of centra, malpositioned arches, extra ribs, arches and halves of centra, small arches and/or fused and/or forked ribs. One fetus each in the control and 0.5 g/kg/day groups had fused sternebrae. Fetus no. 36906-01 in the 1 g/kg/day group had a skull anomaly (fused frontal and nasal bones). No skeletal malformations were observed in the 2 g/kg/day group. The above malformations were not attributed to the test article in the absence of a dose response and their occurrence in control pups.
Skeletal developmental variations were observed across all dose groups, including the control group, and consisted primarily of sternebra (e) nos. 5 and/or 6 unossified, 13th

rudimentary rib(s), 13th full rib(s), 27 presacral vertebrae, stemebra(e) malaligned, hyoid arches bent and 7th cervical rib. These skeletal variations were not attributed to the test article in the absence of a dose-related response and their occurrences in the control group and/or were within the [redacted] historical control data range.

Overall, there appears to be no significant treatment-related fetal external, visceral or skeletal malformations or aberrations. Miralax PEG 3350 did not appear to be teratogenic in this study.

The following table shows the fetal external, visceral and skeletal findings.

Parameter	0 g/kg/day	0.5 g/kg/day	1.0 g/kg/day	2.0 g/kg/day
Fetal External Observation				
Fetuses Examined Externally/litters	151/22	141/23	144/22	88/17
Fetal Visceral Malformation				
Fetuses/Litter Examined	151/22	141/23	144/22	88/17
Abnormal lung lobulation	0	0	0.8	0
Fetal Visceral Variations				
Accessory spleen	11	11	17	6
Major blood vessel variation	9	8	9	4
Retrocaval ureter	3	0	1	2
Gallbladder absent or small	1	1	0	4
Fetal Skeletal Malformations				
Fetuses/Litter Examined	151/22	141/23	144/22	88/17
Vertebral anomaly with or without rib anomaly	2	1	1	0
Sternebre fused	1	1	0	0
Skull anomaly	0	0	1	0
Rib anomaly	1	1	0	0
Fetal Skeletal Variations				
Sternebre malaligned	2	2	1	1
Cervical centrum # 1 ossified				
7th Cervical Rib	3	1	3	1
13th Rudimentary ribs	28	23	28	20
Sternebre #5 and #6 unossified	12	3	9	2
Hyoid arch bent	15	12	12	4
7th Sternebre	0	0	0	1
Reduced ossification of the vertebral arches				
27 Parasacral vertebrae	22	26	39	22
13th Full ribs	37	40	46	32
Extra site of ossification anterior to sternebra # 1	1	2	0	1
Hyoid body and/or arch unossified	0	0	0	1
Sternebre with thread like attachment	3	1	2	0
Accessory skull bone	0	4	1	2

In a Segment II study in New Zealand White rabbits, mated females were treated orally (gavage) with PEG 3350 at 0.5, 1 and 2 g/kg/day. There were no test article-related effects on survival. Treatment-related clinical findings included decreased defecation, soft stool and brown material on the tail at the high dose. In addition, decreased body weight gain and food consumption was observed at high dose during GD 7-21. There were no treatment-related effects on any intrauterine parameters or C-section parameters. No significant treatment-related effects were observed on fetal external, visceral or skeletal parameters at any dose level. Miralax PEG 3350 did not appear to be teratogenic in this study.

Prenatal and Postnatal Development

Study title: Effects of Miralax PEG 3350 on Pre- and Post-natal Development (Segment III) in Rats

Key study findings: In an oral Segment III study with PEG 3350 in rats, four groups of bred female rats (25/sex/group) were administered PEG-3350 by oral gavage (5 ml/kg) from GD 6 through lactation day 20 (36-38 total doses) at 0 (water), 0.5, 1 and 2 g/kg/day. There were no treatment-related effects on F0 survival, clinical condition, body weight, food consumption, gestation length and F1 postnatal survival, body weight, developmental landmarks, startle response, motor activity, learning and memory and reproductive performance, and intrauterine parameter. There were no apparent treatment-related effects on survival of F2 fetuses and external and developmental observations. Miralax PEG 3350 did not appear to have any significant effect on pre- and post-natal development in this study.

Study no.: [redacted] 38203
Volume #, and page #: 17.1-17.5, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: December 5, 2003
GLP compliance: A statement of compliance was included.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: PEG 3350, Lot No. 1275, [redacted]

Methods:

Doses: 0 (water), 0.5, 1 and 2 g/kg/day. The F0 maternal animals were assigned to study groups as follows (from page 20 of the study report). The doses were selected based on the results of the above Segment I and II studies in rats.

Group Number	Test Article	Dosage Level (g/kg/day)	Dosage Concentration (g/mL)	Dosage Volume (mL/kg/day)	Number of Females
1	Vehicle Control	0	0	5	25
2	MiraLax™ PEG-3350	0.5	0.1	5	25
3	MiraLax™ PEG-3350	1	0.2	5	25
4	MiraLax™ PEG-3350	2	0.4	5	25

Species/strain: Rats/Sprague Dawley

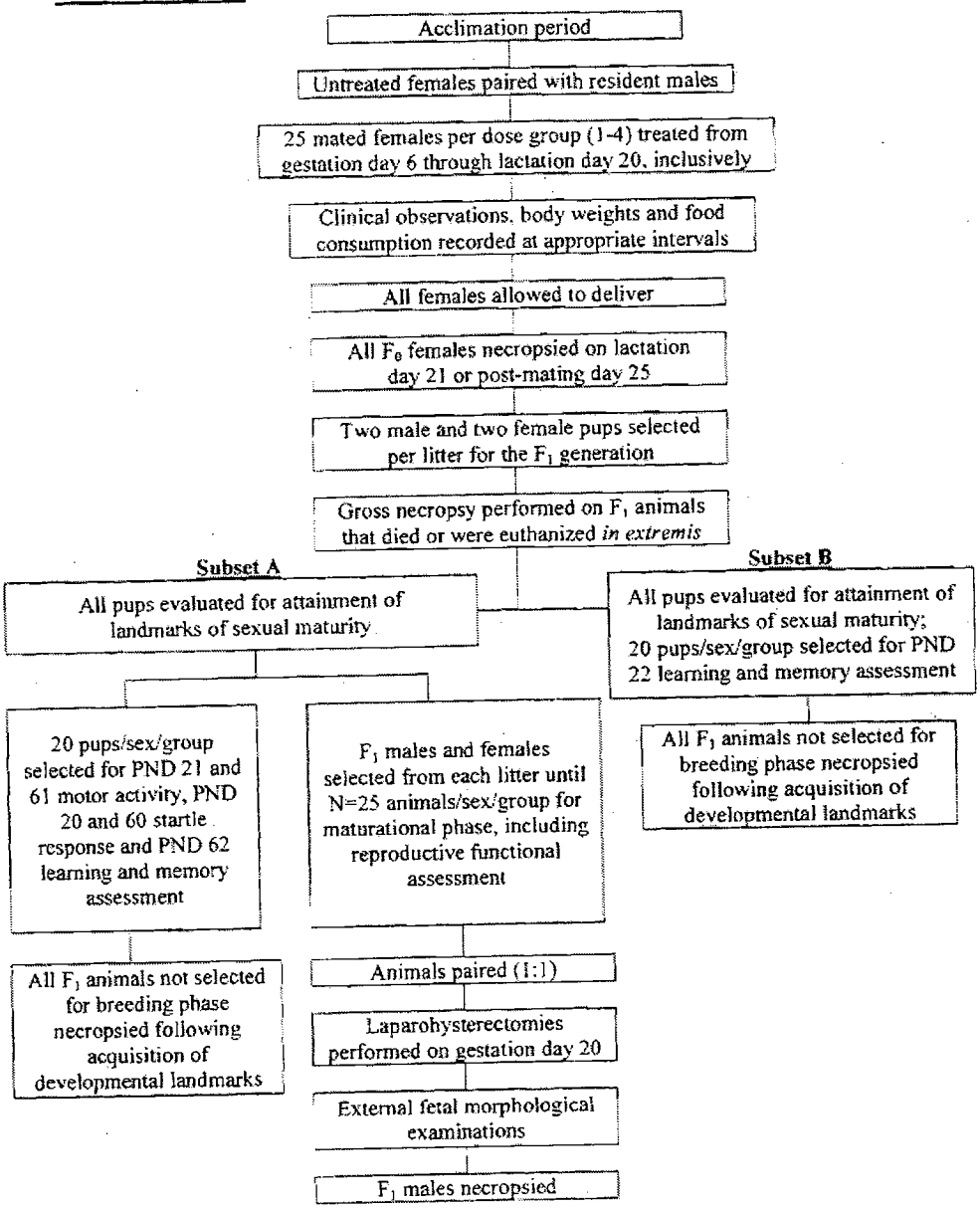
Number/sex/group: 25/dose

Route, formulation, and volume: Oral, solution, 5 ml/kg

Satellite groups used for toxicokinetics: None

Study design: Four groups of bred female rats (25/sex/group) were administered PEG-3350 by oral gavage from GD 6 through lactation day 20 (36-38 total doses) at 0 (water), 0.5, 1 and 2 g/kg/day (5 ml/kg). The following diagram (from page 18 of the study report) shows the study design.

3. STUDY DESIGN



Parameters and endpoints evaluated: All animals were observed twice daily for appearance and behavior. Clinical observations, body weights and food consumption were recorded at appropriate intervals. All females were allowed to deliver and rear their offspring to lactation day 21. Indicators of physical and functional development were evaluated as follows. F1 pups (two males and two

females per litter) were randomly selected for acquisition of developmental landmarks. From these two pups/sex/litter, one male and one female in each litter (until N=20) were selected for locomotor activity on post-natal day 21 (PND 21) and 61, acoustic startle response on PND 20 and 60 and learning and memory assessment on PND 62 (Subset A). The remaining one male and one female selected from each litter (until N=20) were assigned to learning and memory assessment on PND 22 (Subset B). The F1 pups assigned to Subset A and additional males and/or females from each litter (until N=25/sex/group) were assigned to an F1 maturational phase, including reproductive functional assessment. These F1 animals were mated. On gestation day 20, F1 females were necropsied, and fetuses were examined externally for malformations and developmental variations. The F1 males were necropsied following the last laparohysterectomy.

Results:

F_0 in-life: There were no treatment-related mortalities. Soft stool was noted at all doses at 1 hour post-dose. The mean initial and final body weights of control females were 254 and 336 g, respectively. The mean initial and final food consumption of control females were 19 and 72 g/animal/day, respectively. No significant treatment-related changes were observed on body weight, food consumption, pregnancy rate, and mean gestation length.

F_0 necropsy: There were no treatment-related macroscopic findings. Female no. 43501 at 2 g/kg/day group had pale adrenal glands. At the lactation day 21 necropsy, no test article-related effects were observed on the number of pups born, the number of former implantation sites and the number of unaccounted sites. The following table shows the F0 uterine data.

PARAMETER	DOSE (G/KG/DAY)			
	0	0.5	1.0	2.0
Pregnant Dams	25	25	25	25
Implant sites/mean	15.6	16.2	16.2	15.9
Number born/mean	15.1	15.0	15.2	15.1
Unaccounted sites/mean	0.5	1.2	1.0	0.8
Sex at birth (% males/litter)/mean	50.6	50.7	46.7	50.8
Live litter size /mean	15.0	14.9	14.9	14.9

F_1 physical development: The mean number of pups born, live litter size, percentage of males per litter at birth and postnatal survival were unaffected by the F0 treatment. The numbers of F1 pups found dead or missing, as well as the general physical condition of all F1 pups were unaffected by F0 maternal test article administration. The mean initial (PND 1) and final (PND 21) body weights of control males were 7.1 and 53 g,

respectively. The mean initial (PND 1) and final (PND 21) body weights of control females were 6.7 and 50.5 g, respectively. There were no significant treatment-related changes on body weight.

The numbers of pups (litters) found dead from PND 0 through the selection of the F1 generation were 6(4), 3(3), 8(5) and 7(5) at control, 0.5, 1 and 2 g/kg/day, respectively. There were no treatment-related visceral findings at the necropsies of pups that were found dead. One malformation (situs inversus, consisting of laterally transposed organs of the thoracic and abdominal cavities) was noted for pup no. 43388-01 at 0.5 g/kg/day group. Pup no. 43448-0 1 at 1 g/kg/day group had a misshapen heart in which the apex was shorter than normal. Aside from the presence or absence of milk in the stomach, there were no other significant visceral findings.

There were no significant treatment-related visceral findings at the necropsy of pups euthanized on PND 21. Visceral findings consisted of dilated renal pelvis in three pups (nos. 43400-02, 43410-12 and 43435-01) at 1 g/kg/day and one pup (pup no. 4341 7-08) at 2 g/kg/day. This finding was not considered treatment-related, as it was observed in three pups at low dose and in 1 pup at high dose. In addition, the sponsor stated that these were common findings in laboratory rats.

No significant internal findings that could be attributed to F0 maternal treatment at the necropsy of pups (not selected for breeding, Subset B) following acquisition of sexual developmental landmarks. Some of the visceral findings included enlarged spleen (1 of 20 pup at 0.5 g/kg/day), testes (1 of 20 each at 1 and 2 g/kg/day) and lymph nodes (10 of 20, 1 of 20, 4 of 23 and 2 of 20 pups at 0, 0.5, 1 and 2 g/kg/day, respectively), dilated renal pelvis (3 of 20, 1 of 20, 3 of 23 and 0 of 20 at 0, 0.5, 1 and 2 g/kg/day, respectively), white areas on the kidneys (1 of 20 pups at 2 g/kg/day). These were not considered treatment-related in the absence of a dose response and occurrence in control animals.

F_1 behavioral evaluation: The acoustic startle response habituation paradigm was examined on PND 20 and 60 with selected F1 animals (Subset A). There was no treatment-related effect on auditory startle response at any dose level.

Locomotor activity patterns (total activity as well as ambulatory activity counts) in F1 animals (Subset A) were unaffected by F0 maternal treatment with PEG 3350 when evaluated on PND 21 and 61. No remarkable shift in the pattern of habituation was observed at any tested doses when F1 animals were compared to the control group.

There were no biologically meaningful difference in swimming ability during the learning and memory trials between the test article-treated F1 male and female pups at PND 22 and 62. A statistically significant reduction in time to swim the straight channel compared to the control group was noted for the 0.5 g/kg/day group on PND 62; however, this was not considered treatment-related in the absence of a dose response.

F_1 reproduction: No treatment-related effects on F1 reproductive performance was observed at the tested dose levels. Male mating indices were 96.0%, 96.0%, 96.0% and 96.0% and female mating indices were 100.0%, 100.0%, 100.0% and 96.0% in the control, 0.5, 1 and 2 g/kg/day groups, respectively. Male fertility indices were 92.0%, 88.0%, 88.0% and 92.0% and female fertility indices were 96.0%, 92.0%, 92.0% and 92.0% in the same respective groups. Male copulation indices were 95.8%, 91.7%, 91.7% and 95.8% and female conception indices were 96.0%, 92.0%, 92.0% and 95.8% in the control, 0.5, 1 and 2 g/kg/day groups, respectively. The mean numbers of days between pairing and coitus in the test article-treated groups were similar to the control group value (3.6, 3.2, 4.4 and 3.2 days at 0, 0.5, 1 and 2 g/kg/day, respectively). The mean lengths of estrous cycles in these groups were also similar to the control group value (4.3, 4.6, 4.3 and 4.3 day at 0, 0.5, 1 and 2 g/kg/day, respectively). There were no significant treatment-related effects on F1 pre-implantation loss, post-implantation loss, live litter size, fetal body weights, fetal sex ratios and the numbers of corpora lutea and implantation sites. The following table shows the F1 intrauterine data.

PARAMETER	DOSE (G/KG/DAY)			
	0	0.5	1.0	2.0
Pregnant Dams	24	23	23	23
Corpora lutea/dam	18.0 (433/24)	18.7 (431/23)	17.1 (394/23)	18.0 (414/23)
Implant sites/dam	16.0 (383/24)	15.4 (354/23)	16.1 (371/23)	15.8 (364/23)
Pre-implantation loss, mean	2.1	3.3	1.0	2.2
Post-implantation loss, mean	0.7	0.6	0.7	0.6
Resorptions (mean) - Total - early - late	 0.7 0.7 0.0	 0.6 0.6 0.2	 0.7 0.7 0.0	 0.6 0.6 0.0
Live fetuses/dam	15.3	14.8	15.4	15.2
Dead fetuses/dam	0	0	0	0
Fetal weight (g, mean)	3.4	3.4	3.4	3.5

F_2 findings: Intrauterine growth and survival of the F2 fetuses were unaffected by F0 maternal treatment. There were no significant treatment-related effects on F2 fetal external and developmental observations.

In an oral Segment III study with PEG 3350 in rats, four groups of bred female rats (25/sex/group) were administered PEG-3350 by oral gavage (5 ml/kg) from GD 6 through lactation day 20 (36-38 total doses) at 0 (water), 0.5, 1 and 2 g/kg/day. There were no treatment-related effects on F0 survival, clinical condition, body weight, food consumption, gestation length and F1 postnatal survival, body weight, developmental landmarks, startle response, motor activity, learning and memory and reproductive performance, and intrauterine parameter. There were no apparent treatment-related effects on survival of F2 fetuses and external and developmental observations. Miralax PEG 3350 did not appear to have any significant effect on pre- and post-natal development in this study.

2.6.6.7 Local tolerance

None

2.6.6.8 Special toxicology studies

None

2.6.6.9 Discussion and Conclusions

The systemic toxicity of Miralax PEG 3350 was adequately evaluated in a complete range of general toxicity (acute, subacute/subchronic and chronic), genotoxicity, reproductive toxicity, and carcinogenicity studies. Repeated dose toxicity studies were conducted in rodents (mice and rats up to 6 g/kg/day) up to 6 months duration and in non-rodents (dogs up to 3 g/kg/day) up to nine months duration following oral administration.

The target organs of toxicity appeared to vary across species. The major target organ of toxicity in the rat appeared to be the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in males at 6 g/kg/day). In dogs following oral administration of PEG 3350 for 28-days, the target organs of toxicity appeared to be the lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes; foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates), gastrointestinal tract (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue in females at 3, 6 and 9.3 g/kg/day), testes (hypospermia in the epididymides and seminiferous tubule degeneration or multiucleated spermatids of the testes) and salivary gland (atrophy). Following 9-month oral administration of PEG 3350 in dogs (up to 3 g/kg/day), the target organs of toxicity appeared to be testes (retarded development) and prostate (lymphocyte infiltrate) in the males and mammary gland (glandular hyperplasia), liver (vacuolation) and gallbladder (lymphocyte infiltrate and epithelial hyperplasia) in females. The NOAELs could not be determined, as apparent treatment-related effects were seen at all tested doses in mice, rats and dogs.

Miralax PEG 3350 was negative in the Ames test and did not show any clastogenic potential in the chromosome aberration test with human peripheral blood lymphocytes. It was also negative in *in vivo* oral rat micronucleus test. In addition, PEG 3350 was not tumorigenic in mice and rats up to 6 g/kg/day.

In reproductive toxicity studies in rats and rabbits by oral route, Miralax PEG 3350 did not appear to cause any significant adverse effects on the reproductive parameters in either sex. Miralax PEG 3350 did not appear to be teratogenic in rats and rabbits at the tested doses. Miralax PEG 3350 did not cause any effect on pre-and post-natal development in rats up to 2 g/kg/day.

In conclusion, the non-clinical studies conducted with PEG 3350 adequately support its use at the intended therapeutic dosage and in accordance with the proposed product labeling.

2.6.6.10 Tables and Figures

Tables and figures were incorporated in the appropriate sections of the review.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Pivotal toxicology studies were tabulated under section: "**Studies reviewed within this submission**".

OVERALL CONCLUSIONS AND RECOMMENDATIONS

This NDA was submitted to support an Rx-to-OTC switch of MiraLAX laxative for the treatment of occasional constipation. The drug product is composed of only one component, PEG 3350, NF. The average dose is 17 grams of PEG 3350 powder per day in 4-8 ounces of water, juice, soda, coffee or tea.

In this NDA, the sponsor has provided the following studies: pharmacology studies (literature reports); absorption, distribution, metabolism, and excretion studies in rats; safety pharmacology studies; acute oral toxicity study in rats; 3-month oral toxicity study in mice; 3- and 6-month oral toxicity studies in rats; 28-day and 9-month oral toxicity study in Beagle dogs; genotoxicity studies: Ames assay, chromosomal aberration test in cultured human peripheral lymphocytes; rat oral bone marrow micronucleus test; carcinogenicity studies: 104-week oral carcinogenicity study in CD-1 mice and SD rats; reproductive toxicity studies: Segment I and II and Segment III reproductive toxicity studies in the rat and segment II reproductive toxicity studies in the rabbit.

The sponsor did not submit any pharmacology study report. However, the sponsor presented literature references. From the published literature, PEG 3350 acted as an osmotic laxative. As a result of its almost total fecal excretion and its osmotic effects within the colon, it increased stool mass and volume. The increased colonic bulk appeared to stimulate peristalsis. In addition, its action as a surfactant might improve stool passage. PEG 3350 increased fecal dry and wet weight, fecal water output and fecal volume, without increasing the percent of fecal water. It thereby produced a laxative effect consisting of softer, easier to pass stool, with increased stool frequency and water content. PEG did not appear to alter electrolyte balance.

Miralax PEG 3350 was poorly absorbed (0.1-0.2% of the administered dose) and primarily excreted in feces (60-70%) in the rat. Low amount of radioactivity was also found in the bile (0.16% of the dose) of rats. In rats, mean urinary elimination ranged from approximately 10-20% of dose. The terminal half-life ranged from 15-30 hours in rats. The Tmax ranged from 0.5 to 1.0 hour. The main route of excretion was via feces and most of the elimination was occurred over the first 24 hours after treatment. Over the 72-hour period, about 80 and 74% of the administered dose were excreted via feces in males and females, respectively. Overall, results from pharmacokinetic studies using ^{14}C-PEG 3350 indicated that PEG 3350 was poorly absorbed following oral administration, primarily excreted in the feces, and if absorbed, eliminated in the urine.

In an acute oral (gavage) toxicity study in either non bile-duct-cannulated or bile duct-cannulated female rats, the 6 g/kg dose was nonlethal. There was no mortality and significant clinical observations in either non bile-duct-cannulated or bile duct-cannulated animals.

In a 3-month oral gavage study in CD-1 mice, animals were tested at 0 (water), 1.5, 3 and 6 g/kg/day. The target organ of toxicity could be the gastrointestinal tract (small intestine: minimal to mild attenuation of the mucosal epithelium characterized by shortened/fused villi and without crypt gland degeneration; large intestine: minimal to mild attenuation of the mucosal epithelium and luminal distention) in both sexes based on the dose-related increase in incidences of these findings. However, these changes were also observed in some control animals. The NOAEL could not be determined, as treatment-related changes in the gastrointestinal tract were observed at all tested doses in both sexes.

In a 90-day oral gavage study in SD rats, animals were tested with Carbowax PEG 3350 at 1.5, 3.0 and 6.0 g/kg/day. The target organs of toxicity could not be identified in the absence of any significant treatment-related histopathological findings. The NOAEL appeared to be 6 g/kg/day.

In a 6-month oral gavage study in rats, animals were treated with PEG 3350 at 1.5, 3 and 6 g/kg/day. The NOAEL could not be determined, as treatment-related effects were seen at all dose levels. The target organ appeared to be the kidney (focal or multifocal cytoplasmic vacuolation in cortical tubular epithelial cells in 5 of 12 males at 6 g/kg/day).

In a 28-day oral (gavage) toxicity study in Beagle dogs, animals were treated at 3, 6 and 9.3 g/kg/day. The target organs of toxicity appeared to be lungs (minimal to moderate interstitial fibrosis characterized by thickening of alveolar septa with associated pneumocyte hypertrophy/hyperplasia and the presence of a small number of mononuclear inflammatory cells and alveolar histiocytes; foamy or vacuolated histiocytes in perivascular or peribronchiolar regions characterized as perivascular mononuclear infiltrates), gastrointestinal tract (minimal subacute inflammation or crypt abscesses, hemorrhage and lymphoid hyperplasia in cecum, colon, ileum and/or rectum; lymphoid hyperplasia of the gut-associated lymphoid tissue in females at 3, 6 and 9.3 g/kg/day), testes (hypospermia in the epididymides and seminiferous tubule degeneration or

multiucleated spermatids of the testes) and salivary gland (atrophy). The NOAEL could not be determined as treatment-related findings were seen at all dose levels.

In a 9-month oral gavage study in dogs, animals were treated at 0.75, 1.5 and 3 g/kg/day. The target organs of toxicity appeared to be testes (retarded development) and prostate (lymphocyte infiltrate) in the males and mammary gland (glandular hyperplasia), liver (vacuolation) and gallbladder (lymphocyte infiltrate and epithelial hyperplasia) in females. The NOAEL could not be determined, as apparent treatment-related effects were seen at all tested doses.

Miralax PEG 3350 was negative in the Ames test and did not show any clastogenic potential in the chromosome aberration test with human peripheral lymphocytes. It was also negative in *in vivo* oral rat micronucleus test.

In a 104-week oral (gavage) carcinogenicity study in CD-1 mice, animals were treated with Miralax PEG 3350 at 0 (water), 1.5, 3 and 6 g/kg/day. There was a treatment-related decrease in survival for males and females (statistically significant at 1.5 and 6 g/kg/day groups) when compared to the control group by the end of the study. Dose administration in the 6 g/kg/day female group was discontinued during study week 94, when the survival reached the protocol-specified survival of 20 animals within any group and these females were maintained without treatment through study week 104. At week 104, survival in the control, 1.5, 3 and 6 g/kg/day groups was 47%, 25%, 33% and 32%, respectively, for males and 49%, 35%, 39% and 22%, respectively for females. Treatment-related clinical signs included soft feces at 3 and 6 g/kg/day group males and females. There were no test article-related effects on body weights or food consumption. The incidence of palpable masses was unaffected by test article administration. There were no significant test article-related effects on hematology or clinical chemistry parameters. Non-neoplastic microscopic observations included test article-related increased incidence of renal amyloidosis at 6 g/kg/day in females that died or were euthanized *in extremis* compared to the control group animals that died or were euthanized *in extremis*. There were no significant tumor findings in any tissue that could be attributed to treatment with Miralax PEG 3500.

In a 104-week oral (gavage) carcinogenicity study in SD rats, animals were treated with Miralax PEG 3350 at 0 (water), 1.5, 3 and 6 g/kg/day. There was no significant impact on overall survival. Clinical signs included increased incidences of soft feces and brown material (dry and/or wet) on the urogenital and/or anogenital areas at 3 and 6 g/kg/day group males and the 1.5, 3 and 6 g/kg/day group females. Treatment-related histopathological changes were observed in the kidney (chronic progressive nephropathy, vacuolation, hyperplasia of clear cell and tubule cell), urinary bladder (cytoplasmic vacuolation, of the superficial transitional cell layer), colon (glandular atrophy associated with dilatation), adrenal medulla (hyperplasia) and liver (basophilic and clear cell foci). There were no treatment-related tumor findings in any tissue that was attributed to treatment with Miralax PEG 3500. Overall, the results appeared to be negative for any tumor findings.

In a Segment I study in rats, males and females were treated at 0, 0.5, 1.0 and 2.0 g/kg/day. Male and female survival was unaffected by test article administration in all dose groups. No treatment-related effects were observed on mean body weights, food consumption and organ weights at any of the tested doses. No test article-related effects were observed on male or female reproductive parameters (estrous cycles, mating and fertility indices) or on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate, sperm motility and sperm morphology). Intrauterine survival (pre- and post-implantation losses, viable embryos and numbers of corpora lutea and implantation sites) was unaffected by test article administration at all dose levels.

In a Segment II study in rats, mated females were treated orally (gavage) with PEG 3350 at 0.5, 1 and 2 g/kg/day. No test article-related effects were observed at any dose level on survival, body weights, and food consumption. There were no significant treatment-related effects on any intrauterine parameters or C-section parameters. No significant treatment-related effects were observed on fetal external, visceral or skeletal parameters at any dose level. PEG 3350 did not appear to be teratogenic in this study.

In a Segment II study in New Zealand White rabbits, mated females were treated orally (gavage) with PEG 3350 at 0.5, 1 and 2 g/kg/day. There were no test article-related effects on survival. Treatment-related clinical findings included decreased defecation, soft stool and brown material on the tail at the high dose. In addition, decreased body weight gain and food consumption was observed at high dose during GD 7-21. There were no treatment-related effects on any intrauterine parameters or C-section parameters. No significant treatment-related effects were observed on fetal external, visceral or skeletal parameters at any dose level. Miralax PEG 3350 did not appear to be teratogenic in this study.

In an oral Segment III study with PEG 3350 in rats, four groups of bred female rats (25/sex/group) were administered PEG-3350 by oral gavage (5 ml/kg) from GD 6 through lactation day 20 (36-38 total doses) at 0 (water), 0.5, 1 and 2 g/kg/day. There were no treatment-related effects on F0 survival, clinical condition, body weight, food consumption, gestation length and F1 postnatal survival, body weight, developmental landmarks, startle response, motor activity, learning and memory and reproductive performance, and intrauterine parameter. There were no apparent treatment-related effects on survival of F2 fetuses and external and developmental observations. Miralax PEG 3350 did not appear to have any significant effect on pre- and post-natal development in this study.

The systemic toxicity of Miralax PEG 3350 was adequately evaluated in a complete range of general toxicity (acute, subacute and chronic), genotoxicity, reproductive toxicity, and carcinogenicity studies. Miralax PEG 3350 was not genotoxic. In addition, Miralax PEG 3350 was not tumorigenic in 104-week studies in mice and rats. In fertility and reproductive performance study in rats, Miralax PEG 3350 did not cause any adverse effect. It was also not teratogenic in rats or rabbits. Therefore, from a preclinical standpoint, this NDA may be approved.

Conclusions: From a preclinical standpoint, this submission meets the guidelines and satisfies the criteria for marketing authorization of Miralax PEG 3350 as an Over-the-Counter drug and appears to be safe for the proposed use.

Unresolved toxicology issues: None

Recommendations: From a preclinical standpoint, this submission meets the guidelines and satisfies the criteria for marketing authorization of Miralax PEG 3350 as an Over-the-Counter drug and appears to be safe for the proposed use.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc:

Original NDA
HFD-180
HFD-560/RPM/LCDR Olin
HFD-180/Dr. Choudary
HFD-180/Dr. Chakraborti
HFD-048/Dr. Viswanathan

R/D Init. J Choudary: 6/30/06

APPENDIX/ATTACHMENTS

Appendix-1: List of Non-Neoplastic and Neoplastic Lesions for the Mouse study, page: 136

Appendix-2: List of Non-Neoplastic and Neoplastic Lesions for the Mouse study, page: 280

288 Page(s) Withheld

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PHARMACOLOGIST

Jasti Choudary
7/13/2006 02:46:43 PM
PHARMACOLOGIST