Table 26: Abnormal laboratory results among subjects with two or more consecutive abnormal values in Protocol 851-CR1*

Laboratory Test*	Abnormal change from baseline	851-CR1 subjects		851-CR3 subjects MiraLax (N = 311) N (%)	All MiraLax subjects (%) (N = 515)
		Placebo (N = 100) N and %	MiraLax (N = 204) N (%)		
ALT	Normal to high	1	7 (3.4)	11 (3.5)	3.5
	High to higher	1	2 (1.0)	1 (0.3)	0.6
	High to less high/normal	2	1 (0.5)	4 (1.3)	1.0
AST	Normal to high	3	3 (1.5)	4 (1.3)	1.4
	High to higher	0	2 (1.0)	3 (1.0)	1.0
	High stable or less high	1	1 (0.5)	3 (1.0)	0.8
Amylase	Normal to high	1	1 (0.5)	2 (0.6)	0.6
	High to higher	0	3 (1.5)	4 (1.3)	1.4
	High to less high or stable	4	9 (4.4)	13 (4.2)	4.3
	Normal to low / low	2	10 (4.9)	12 (3.9)	4.3
Bicarbonate	Normal to low	9	13 (6.4)	13 (4.2)	5.0
	Normal to high	0	1 (0.5)	4 (1.3)	1.0
	High stable	1	1 (0.5)	0	0.2
	Low to lower	1	8 (3.9)	4 (1.3)	2.3
	Low to higher or stable	1	6 (2.9)	5 (1.6)	2.1
Blood urea nitrogen	Normal to high	1	6 (2.9)	2 (0.6)	1.6
	High to higher	1	1 (0.5)	1 (0.3)	0.4
	High stable	2	0	8 (2.6)	1.6
Calcium	Normal to high	1	4 (2.0)	5 (1.6)	1.7
	High to higher	1	0	5 (1.6)	1.0
	High to less high or stable	2	4 (2.0)	8 (2.6)	2.3
	Normal to low	0	0	3 (1.0)	0.6
Chloride	Normal to high	5	10 (4.9)	12 (3.9)	4.3

Table 26: Abnormal laboratory results among subjects with two or more consecutive abnormal values in Protocol 851-CR1*

Laboratory Test*	Abnormal change from baseline	851-CR1 subjects		851-CR3 subjects MiraLax (N = 311) N (%)	All MiraLax subjects (%) (N = 515)
		Placebo (N = 100) N and %	MiraLax (N = 204) N (%)		
	High to higher	0	1 (0.5)	3 (1.0)	0.8
	High stable	3	8 (3.9)	15 (4.8)	4.5
	Normal to low/low stable	1	2 (1.0)	4 (1.3)	1.2
Creatine kinase	Normal to high	1	2 (1.0)	0	0.4
	High to higher	3	0	4 (1.3)	0.8
	High to less high or stable	4	3 (1.5)	4 (1.3)	1.4
	Normal to low / low	8	6 (2.9)	10 (3.2)	3.1
Creatinine	Normal to high	0	0	4 (1.3)	0.8
	High to higher	1	4 (2.0)	5 (1.6)	1.7
	High stable	1	2 (1.0)	7 (2.3)	1.7
GGT	Normal to high	6	2 (1.0)	9 (2.9)	2.1
	High to higher	2	11 (5.4)	15 (4.8)	4.1
	High stable	4	1 (0.5)	9 (2.9)	1.9
	High to less high	9	9 (4.4)	25 (8.0)	6.6
Magnesium	Normal to low	1	0	0	0
	Normal to high	0	0	3 (1.0)	0.6
	High to higher	1	1 (0.5)	2 (0.6)	0.6
	High stable or less high	1	1 (0.5)	3 (1.0)	0.8
	Low stable	1	0	0	0
Phosphate	Normal to high	3	24 (11.8)	21 (6.8)	8.7
	High to higher	2	3 (1.5)	5 (1.6)	1.6
	High stable or less high	7	13 (6.4)	17 (5.5)	5.8
	Normal to low	1	6 (2.9)	0	1.2
Potassium	Normal to high	2	2 (1.0)	2 (0.6)	0.8
	High to higher	2	1 (0.5)	2 (0.6)	0.6

Table 26: Abnormal laboratory results among subjects with two or more consecutive abnormal values in Protocol 851-CR1*

Laboratory Test*	Abnormal change from baseline	851-CR1 subjects		851-CR3 subjects MiraLax (N = 311) N (%)	All MiraLax subjects (%) (N = 515)
		Placebo (N = 100) N and %	MiraLax (N = 204) N (%)		
	High stable or less high	1	1 (0.5)	3 (1.0)	0.8
	Normal to low	3	0	1 (0.3)	0.2
Sodium	Normal to low	5	10 (4.9)	10 (3.2)	3.9
	Low to lower	0	2 (1.0)	3 (1.0)	1.0
	Low to higher	1	3 (1.5)	5 (1.6)	1.6
	Low stable	1	4 (2.0)	2 (0.6)	1.2

* Cholesterol, triglycerides, and glucose vary widely with timing of food. Subjects did not have their blood drawn fasting or consistently at a certain time after a meal; therefore, results for these tests are difficult to interpret.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Subjects who discontinued the study early due to laboratory abnormalities are presented in Table 27 below.

Table 27: Subjects discontinued early due to abnormal laboratory results

Study subject (treatment)	Demographic	Study Day	Abnormal lab	Comment
Study 851-CR1				
101-10 (MiraLax)	M, 22 yo, Cauc.	32	Elevated CPK	
119-06 (MiraLax)	F, 48 yo Cauc.	119	Low hematocrit Elevated LFTs	
113-04 (placebo)	F, 75 yo, Cauc.	28	Low hematocrit	Diagnosed with gastric cancer.
Study 851-CR3				
108-80 (MiraLax)	M, 38 yo Cauc.	1	Elevated TSH	Newly diagnosed hypothyroidism
134-147 (MiraLax)	F, 63 yo Cauc.	1	Abnormal TSH	
137-33 (MiraLax)	M, 37 yo Cauc.	57	Increased ALT	
149-402 (MiraLax)	M, 86 yo Cauc.	158	Anemia	Check – D/C may have bee due to diarrhea and not anemia

Many subjects who participated in Studies 851-CR1 and 851-CR3 came into the studies with abnormal liver function tests, elevated cholesterol and triglycerides, and intermittently abnormal glucose uric acid levels. Some subjects had mildly elevated but stable liver enzymes. Among subjects who persistently or intermittently displayed abnormal laboratory values, there were no trends indicating a worsening condition or a clinically concerning condition during the study periods. Two subjects had a single serum sodium value in the mid-120 range. Some potassium levels were in the 30 range which is incompatible with life and probably indicates blood sample hemolysis.

Tables 28 and 29 present a summaries of experimental laboratory ranges with highest and lowest laboratory values for placebo and MiraLax treated populations from 851-CR1 and 851-CR3. A more detailed description of subjects with extreme outlying laboratory values is provided in the appendices, section 10.5. The sponsor provided this line listing of the most abnormal laboratory results.

Table 28: Comparison of the highest and lowest values for electrolytes, BUN, creatinine, and liver/muscle enzymes among placebo and MiraLax treated subjects in Studies 851-CR1 and 851-CR3*

Laboratory Test (normal range)	Assessment	851-CR1: Placebo	851-CR1: MiraLax	851-CR3: MiraLax
Bicarbonate (23 – 29 mEq/dL)	Range (baseline)	21 – 31	5 – 31	18 – 32
	Highest value (visit)	36 (visit 4)	33 (visit 3)	35 (visit 4)
	Lowest value (visit)	18 (visit 2)	18 (visits 3, 4, 5)	16 (visit 5)
Blood urea nitrogen (6 – 20 mg/dL)	Range (baseline)	5 – 39	5 – 31	6 – 43
	Highest value (visit)	39 (base)	40 (visit 6)	52 (visit 2)
Calcium (8.6 – 10.0 mg/dL)	Range (baseline)	8.6 – 10.7	8.5 – 10.9	8.5 – 11.5
	Highest value (visit)	10.7 (base, visit 4)	10.9 (base)	11.5 (base)
	Lowest value (visit)	8.5 (visit 5)	8.4 (visits 2, 5)	6.6 (visit 2)
Chloride (98 – 107 mEq/dL)	Range (baseline)	96 – 109	93 – 115	92 – 111
	Highest value (visit)	114 (visit 2)	115 (base)	116 (visit 3)
	Lowest value (visit)	94 (visits 5, 6)	90 (visit 2)	92 (base)
Creatinine (0.6 – 1.1 mg/dL)	Range (baseline)	0.5 – 1.9	0.5 – 1.8	0.4 – 2.9
	Highest value (visit)	2.3 (visit 2)	2.1 (visit 6)	3.7 (visit 6)
Magnesium (1.6 – 2.6 mg/dL)	Range (baseline)	1.5 – 2.6	1.8 – 2.7	1.0 – 3.1
	Highest value (visit)	2.7 (visit 3)	2.7 (base)	3.1 (base)
	Lowest value (visit)	1.5 (base, visit 2)	1.4 (visit 2)	0.1 (visit 3)**
Phosphate (2.7 – 4.5 mg/dL)	Range (baseline)	2.7 – 5.5	2.3 – 5.5	2.1 – 5.2
	Highest value (visit)	5.5 (base, visit 2)	6.3 (visits 2, 5)	5.6 (visits 3, 6)
	Lowest value (visit)	2.3 (visit 2)	2.2 (visit 6)	2.1 (base, visits 2, 4)
Potassium (3.5 – 5.1 mEq/dL)	Range (baseline)	3.3 – 5.9	3.1 – 5.9	3.2 – 5.7
	Highest value (visit)	7.6 (visit 2)	5.9 (base, visit 5)	Lab error (values > 25)
	Lowest value (visit)	3.0 (visit 5)	3.1 (base)	3.2 (base, visits 1,2)
Sodium	Range (baseline)	130 - 144	129 – 146	130 - 147

Table 28: Comparison of the highest and lowest values for electrolytes, BUN, creatinine, and liver/muscle enzymes among placebo and MiraLax treated subjects in Studies 851-CR1 and 851-CR3*

Laboratory Test (normal range)	Assessment	851-CR1: Placebo	851-CR1: MiraLax	851-CR3: MiraLax
(136 – 145 mEq/dL)	Highest value (visit)	151 (visit 2)	156 (visit 3)	150 (visit 3)
	Lowest value (visit)	130 (base, visit 2)	128 (visit 4)	126 (visit 5)
ALT (10 – 28 IU/L)	Range (baseline)	8 – 104	8 – 103	8 - 119
	Highest value (visit)	110 (visit 5)	137 (visit 6)	207 (visit 5)
Amylase 36 – 128 IU/L)	Range (baseline)	15 – 265	17 – 394	15 - 232
	Highest value (visit)	273 (visit 2)	394 (base)	345 (visit 4)
AST (13 – 35 IU/L)	Range (baseline)	14 – 74	13 – 62	14 - 99
	Highest value (visit)	80 (visit 5)	77 (visit 5)	152 (visit 5)
Creatine kinase (49 – 234 IU/L)	Range (baseline)	21 – 648	24 – 1770	21 - 1042
	Highest value (visit)	994 (visit 2)	1770 (base)	1694 (visit 3)
GGT (2 – 24 IU/L)	Range (baseline)	9 – 200	9 – 289	9 - 199
	Highest value (visit)	357 (visit 5)	414 (visit 5)	317 (visit 5)

*All electrolytes and renal functions are included. Liver function tests and other enzyme tests are included if the highest value was three times the upper limit or more. Cholesterol, triglycerides, and glucose were not included as time of assessment with regard to food intake was not specified or consistent.
** The lower limit of range of values for serum magnesium provided by the sponsor for Study 851-CR3, visits 2, 3, 4, and 5 were extremely low. It is not clear if this represents laboratory error. Only 8 subjects of 311 in this study had two consecutive abnormal magnesium levels.

Table 29: Comparison of the highest and lowest values for hematology assessments and urine specific gravity among placebo and MiraLax treated subjects in Studies 851-CR1 and 851-CR3*

Laboratory Test (normal range)	Assessment	851-CR1: Placebo	851-CR1: MiraLax	851-CR3: MiraLax
WBC ($4.5 - 11.0 \times 10^3/\mu L$)	Range (baseline)	3.7 – 11.3	3.1 – 12.3	2.5 – 17.5
	Highest value (visit)	20.5 (visit 5)	14.7 (visit 6)	17.5 (base)
	Lowest value (visit)	2.0 (visit 5)	3.0 (visit 2)	2.2 (visit 3)
Hematocrit (35.0 – 47.0 %)	Range (baseline)	31.7 – 52.7	32.4 – 50.3	28.5 – 51.7
	Highest value (visit)	52.7 (base)	50.3 (base)	51.7 (base)
	Lowest value (visit)	27.5 (visit 4)	29.1 (visit 3)	25.1 (visit 3)
Platelets ($150 - 400 \times 10^3/\mu L$)	Range (baseline)	131 – 517	137 – 519	15[¤] - 586
	Highest value (visit)	815 (visit 5)	533 (visit 2)	846 (visit 3)
	Lowest value (visit)	124 (visit 5)	122 (visit 5)	108 (visit 6)
Urine specific gravity (1.002 – 1.030)	Range (baseline)	1.02 – 1.03	1.01 – 1.03	1.01 – 1.03
	Highest value (visit)	1.03 (all)	1.03 (all)	1.03 (all)
	Lowest value (visit)	1.02 (all)	1.01	1.01 (all)

*All electrolytes and renal functions are included. Liver function tests and other enzyme tests are included if the highest value was three times the upper limit or more. Cholesterol, triglycerides, and glucose were not included as time of assessment with regard to food intake was not specified or consistent.
** The lower limit of range of values for serum magnesium provided by the sponsor for Study 851-CR3, visits 2, 3, 4, and 5 were extremely low. It is not clear if this represents laboratory error. Only 8 subjects of 311 in this study had two consecutive abnormal magnesium levels.
[¤]The low value of 15,000 for platelets for study 851-CR3 was a reported result; however, when the subject was called in for a repeat test, the result was normal.

7.1.7.4 Additional analyses and explorations

None.

7.1.7.5 Special assessments

None.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Study personnel measured subjects' weights and vital signs at the enrollment visits and end of study visits for Studies 851-CR1, 851-CR3, and 851-ZCC. Only 851-CR1 has a placebo control. These studies were of different duration (6 months, 12 months, and 1 month respectively) and can provide some comparison of vital sign effects with MiraLax treatment over different durations of use.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Since Study 851-CR1 was the only study with a placebo control and since vital signs measurements were taken at only two time points, this information is summarized in Table 30 below.

7.1.8.3 Standard analyses and explorations of vital signs data

Table 30: Vital signs for subjects treated with MiraLax or placebo in Studies 851-CR1, 851-CR3, and 851-ZCC

Assessment	Visit	Statistic	851-CR1		851-CR3	851-ZCC
			Placebo	MiraLax	MiraLax	MiraLax
			N = 100	N = 204	N = 311	N = 120
Weight (kg)	Screening	N	99	200	309	117
		Mean	**75.09**	**74.66**	**77.29**	**77.02**
		SD	15.56	16.25	17.63	22.38
		Range	**40 – 113**	**46 – 147**	**46 – 159**	**50 – 204**
	End of Study	N	85	188	242	108
		Mean	**74.98**	**74.99**	**77.82**	**76.64**
		SD	15.69	16.34	18.41	22.44
		Range	**40 – 111**	**46 – 135**	**40 – 150**	**47 – 204**
	Change	N	84	184	242	105
		Mean	0.79	0.22	0.19	0.10
		SD	2.56	3.26	4.82	2.36
		Range	-6 – 12	-15 – 12	-23 – 40	-7 – 17
Temperature (°F)	Screening	N	98	200	301	118
		Mean	**97.76**	**97.84**	**97.73**	**97.77**
		SD	0.72	0.69	0.73	0.70
		Range	**95.9 – 100.2**	**95.0 – 99.6**	**95.6 – 99.7**	**95.6 – 99.3**
	End of Study	N	83	187	232	108
		Mean	**97.79**	**97.70**	**97.78**	**97.78**
		SD	0.72	0.66	0.74	0.73
		Range	**95.5 – 100.0**	**95.4 – 99.5**	**93.6 – 99.6**	**95.4 – 99.2**
	Change	N	81	183	225	106
		Mean	0.04	-0.12	0.06	-0.01
		SD	0.71	0.78	0.92	0.76
		Range	-1.8 – 1.4	-.0 – 2.1	-4.0 – 2.3	-3.1 – 2.0
Pulse (bpm)	Screening	N	97	202	310	119
		Mean	**70.81**	**71.01**	**70.95**	**70.58**
		SD	10.08	9.17	9.00	9.96
		Range	**48 – 100**	**50 – 100**	**50 – 96**	**43 – 104**
	End of Study	N	85	188	242	108
		Mean	**72.84**	**72.41**	**71.90**	**72.26**
		SD	11.08	10.12	9.57	10.59
		Range	**48 – 110**	**47 – 104**	**44 – 108**	**48 – 108**
	Change	N	82	186	241	107
		Mean	2.29	1.25	0.89	2.12
		SD	9.37	11.25	10.17	10.76
		Range	-20 – 23	-32 – 38	-30 – 36	-22 – 38
Systolic blood Pressure (mm Hg)	Screening	N	99	202	311	119
		Mean	**125.24**	**121.62**	**125.05**	**118.05**
		SD	18.28	14.97	16.08	16.14
		Range	**90 – 170**	**90 – 177**	**90 – 172**	**76 – 168**
	End of Study	N	85	189	245	108
		Mean	**121.58**	**119.68**	**123.89**	**116.08**
		SD	14.44	14.63	15.09	14.95
		Range	**90 – 150**	**90 – 188**	**90 – 172**	**84 – 152**

Table 30: Vital signs for subjects treated with MiraLax or placebo in Studies 851-CR1, 851-CR3, and 851-ZCC

Assessment	Visit	Statistic	851-CR1		851-CR3	851-ZCC
			Placebo	MiraLax	MiraLax	MiraLax
			N = 100	N = 204	N = 311	N = 120
	Change	N	84	187	245	107
		Mean	-4.06	-2.56	-2.67	-2.30
		SD	17.11	14.53	14.97	11.96
		Range	-50 – 38.0	-42 – 68	-60 – 31	-32 – 28
Diastolic blood pressure (mm Hg)	Screening	N	99	202	311	119
		Mean	**76.38**	**75.52**	**75.63**	**75.03**
		SD	11.49	9.21	9.10	8.62
		Range	**40 – 105**	**50 – 100**	**53 – 100**	**56 – 100**
	End of Study	N	85	189	245	108
		Mean	**74.71**	**73.84**	**74.71**	**74.17**
		SD	8.96	9.41	9.54	9.97
		Range	**54 – 94**	**52 – 102**	**52 – 110**	**52 – 99**
	Change	N	84	187	245	107
		Mean	-1.76	-1.8	-1.43	-1.18
		SD	10.47	8.77	10.27	8.00
		Range	-27 – 30	-30 – 22	-30 – 29	-26 – 15

7.1.8.3.1 Analyses focused on measures of central tendencies

As shown in Table 30, there were no clinically significant changes in mean values for weight, temperature, pulse, or blood pressure when measured at the enrollment and end of study visits for all three clinical studies. All mean values were within the normal range.

Mean weight increased or decreased by no more than 0.5 kg from the beginning to the end of the studies in all placebo and MiraLax treated groups. The maximum weight in the weight range declined at the end of the study for subjects treated with MiraLax in 851-CR1 and 851-CR3 but it is not clear whether this was due to weight loss in ongoing participants or early discontinuation of the heaviest subjects. The minimum weight was stable during the course of the study for placebo and MiraLax treatment groups in Study 851-CR1.

There were no clinically significant changes in temperature or pulse during the three clinical studies. Mean heart rate changed less than 2 beats per minute for all three MiraLax treatment groups. From the beginning to the end of study 851-CR1, change in mean pulse was less for the MiraLax treated group than the placebo treated group with a smaller standard deviation. Heart rates fell within a clinically acceptable range for all three studies.

Means and ranges for systolic (SBP) and diastolic blood pressure (DBP) measurements at enrollment and end of study were similar with small decreases seen in mean values and often in the maximum values. The largest decrease was seen for the placebo treated group where the mean SBP decreased by more than 3.5 mm Hg. The MiraLax treated groups from Studies 851-CR1, 851-CR3, and 851-ZCC experienced a mean SBP decrease of less than 2 mm Hg. All placebo and MiraLax treatment groups experienced a mean decrease in

DBP of 1 – 2 mm Hg.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Overall, the vital sign data suggest few clinically significant changes. However, the weight range data suggested a couple of significant weight decreases in MiraLax treated subjects from Studies 851-CR3 and 851-ZCC. These subjects are described here:

- In Study 851-CR3, an 81 year old African American female with multiple medical problems decreased her weight from 46 kg at the beginning of the study to 40 kg at the end of the study. Medical problems included hypertension, cardiac arrhythmia, pernicious anemia, hypothyroidism, and gastroesophageal reflux disease. Adverse events included an upper respiratory infection that was treated with ampicillin, abdominal pain, and sore gums. She did not experience diarrhea. Looking at starting and ending weights for other subjects weighing 55 kg or less, weights were stable within 1 kg.

- In Study 851-ZCC, there was a 29.5 year old Asian female whose weight decreased from 50 kg to 47 kg during the 28 days of the study. Her medical history was significant for constipation and seasonal allergies, and her only medications were allergy shots and a cough suppressant. She did not report any adverse events during the study and did not use bisacodyl.

In the 851-CR1 MiraLax treatment arm, the maximum SBP value increased from 177 to 188 mm Hg and in Study 851-CR3, the maximum DBP value increased from 100 to 110 mm Hg. Subject subpopulations with SBP > 140 and /or DBP > 90 for one or both measurements are presented in Table 31.

Table 31: Subjects with SBP > 140 mm Hg and/or DBP > 90 mm Hg at end of study visit

		851-CR1		851-CR3	851-ZCC
		Placebo	**MiraLax**	**MiraLax (N = 251)**	**MiraLax (N = 108)**
Baseline	High BP N (%)	23 of 100 (23.0)	24 of 204 (11.8)	59 of 311 (19.0)	6 of 120* (5.0)
	Preexisting hypertension	10 (43.5)	11 (45.8)	40 (67.8)	4 (66.7)
End of Study	High BP N (%)	4 of 80 (5.0)	15 (8.1)	33 (13.1)	6 (5.5)*
	Preexisting hypertension	2 (50)	7 (46.7)	20 (60.6)	2 (33.3)
Comments		2 subjects without HTN had anxiety; 1 used Viagra	3 subjects without HTN had anxiety; 1 took pseudoephedrine daily	1 subject without HTN had anxiety	1 subject without HTN used a sympathomimetic drug

In all cases but one, subjects with the maximum SBP and DBP readings were those with a pre-existing diagnosis of hypertension. There were nine subjects in the MiraLax treatment arm of 851-CR1, 12 subjects from 851-CR3, and 3 subjects from 851-ZCC who had an elevated SBP and/or DBP reading at the end of study assessment following a normal BP at their baseline visit. Most of these elevations were mild except for subject 142-11 from 851-CR1 who had a blood pressure reading of 188/87. It is not possible to determine whether these one-time blood pressure measurements are signs of new onset hypertension in these individuals or isolated events due to human error, other medications, or situational anxiety.

In Study 851-CR1, all nine subjects with a normal BP reading at baseline and a high BP reading at the end of the study were in the MiraLax treatment group. Two factors may have contributed to this imbalance: the placebo treatment group had a higher percentage of subjects with elevated BP at baseline and a higher rate of early discontinuation due to lack of efficacy. Given the minimal change in blood pressure statistics overall, it does not appear that use of MiraLax over 1, 6, or 12 months increases the incidence of hypertension.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No subjects discontinued from Studies 851-CR1, 851-CR3, or 851-ZCC for abnormal vital signs. See section 7.1.8.3.3 for a discussion of outliers.

7.1.8.4 Additional analyses and explorations

None.

7.1.9 Electrocardiograms (ECGs)

Not applicable.

7.1.10 Immunogenicity

Polyethylene glycol is considered a non-toxic, non-immunogenic, non-antigenic polymer. Researchers attach PEG chains to proteins, peptides, and non-peptide molecules to reduce

their immunogenicity.[14] The sponsor did not submit data specifically addressing immunogenicity. The prescription MiraLax label notes that patients using other PEG-containing medicines have occasionally developed urticaria suggestive of an allergic reaction. Post-marketing data submitted by the sponsor contains hypersensitivity reactions.

This reviewer searched the literature and was not able to find any published cases of allergic reaction to a high molecular weight PEG. Two articles reported allergic reactions to topical exposure to low molecular weight liquid PEGs (M.W. 200 – 700) that are often used as solvents for topical medicine products. One article reported four patients who developed immediate urticarial reactions upon product application, and two patients who developed delayed allergic eczematous reactions. Allergic cross reactions have occurred between PEGs 200, 300, and 400, which are all liquid PEGs, but not between these lower molecular weight PEGs and the higher molecular weight (1000 – 6000) solid PEG products.[15] In 1975, Hannuksela et al documented an allergy to PEG 400 in 0.3% of 1556 subjects with eczema.[16]

7.1.11 Human Carcinogenicity

No human carcinogenicity data were submitted with the application.

7.1.12 Special Safety Studies

None.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This reviewer was unable to find any data suggesting a physiological dependence or withdrawal phenomenon occurring with PEG use. The sponsor states that there is no evidence that PEG 3350 is metabolized by the human body or that it can be used to alter the conscious state. Since the approval of MiraLax in 1999, the sponsor has not received any post-marketing reports of MiraLax abuse.

All laxative agents have abuse and misuse potential. Individuals with constipation usually experience recurrent or chronic constipation, whether they treat their symptoms with

[14] Veronese FM, Pasut G. PEGylation, successful approach to drug delivery. Drug Discov Today 2005 Nov 1; 10(21): 1451 – 8.
[15] Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. Contact Dermatitis 1978 Jun; 4: 135.
[16] Hannuksela M, Pirila V, Salo OP. Skin reactions to propylene glycol. Contact Dermatitis 1975; 1(2): 112 – 6.

laxatives occasionally or chronically. Frequent use of some laxative drugs leads to a physiological dependence on the laxative in order to have a BM. Thus far, this phenomenon has not been described with PEG 3350, and a PubMED search does not produce any citations suggesting development of a physiological dependence with PEG use. Individuals with eating disorders (including anorexia, bulemia, and binge-eating disorder) may use laxatives in attempt to pass food through the body quickly, thereby decreasing caloric absorption. The sponsor states that individuals with eating disorders are unlikely to choose PEG 3350 as their laxative of choice for purging, because it takes one to four days to achieve a bowel movement. This reviewer conducted a PubMED search using the following search terms:

PEG and eating disorders
PEG and anorexia
PEG and bulemia
Polyethylene glycol and anorexia.

No citations were found.

Upon FDA request for additional information regarding abuse potential, the sponsor submitted a report on MiraLax overdose and abuse potential from the American Association of Poison Control Centers (AAPCC). This database search and report were requested by Braintree for the years 1999 – 2005, the dates from product approval up to the current time. The AAPCC cautions in their report that the data obtained from the search on *Human Exposure to MiraLax* is vast and inconsistent with many uncontrolled variables. In addition, while MiraLax is mentioned in each cited phone call, the actual substance (exposure agent) that prompted the call to the Poison Control Center is unknown.

In their reports, the AAPCC uses a *substance count* (range 1 – 11) and *number of substances* (range 1 – 19) to help define the likelihood that the agent under study is the exposure agent. The higher MiraLax is in the substance count and the number of substances list, the more likely it is that MiraLax was the exposure agent that triggered the call to the Poison Control Center.

Based on reported human data with MiraLax, the AAPCC defined a MiraLax overdose as any case report of exposure to a dose greater than 34 grams, double the recommended 17 g dose. Abuse potential was defined as any case report with the reason for exposure classified as *intentional*. The overdose data will be presented in section 7.1.16 below.

The AAPCC database search identified 17 case reports that could possibly represent MiraLax abuse. All cases identified ingestion as the route of administration. Cases were classified as follows:

- Intentional – abuse (2 cases)
- Intentional – misuse (7 cases)
- Intentional – suspected suicide (6 cases)
- Intentional – unknown (2 cases).

Sixteen of 17 exposure sites were residential and one was not specified. Nine of the 17 cases identified the substance count for MiraLax as "1," and six cases listed MiraLax as the most likely exposure agent. The *Total Number of Substances* ranged from 1 – 19.

Nine subjects were adults 26 – 81 years of age, and seven were children between five months and 16 years of age. There was one case in a five month old, 2 cases in children ages 2 – 11 years, and 4 cases in adolescents. Fourteen of 17 cases were female.

Among nine intentional abuse or misuse cases, four subjects used MiraLax chronically and acutely misused or abused the drug. Four of the six cases considered intentional suspected suicide attempts also used MiraLax chronically. Data on quantity of MiraLax consumed was incomplete but available information suggests that cases used 9 – 51 g of MiraLax.

Eight of the 17 cases experienced no clinical effects from taking the identified substances. Seven out of these eight cases identified MiraLax as the most likely exposure agent and for six, it was the only drug used. The remaining nine cases experienced a total of 24 clinical events listed below in Table 32, and all but five were classified as *related* to the drug exposure(s):

Table 32: Clinical effects of MiraLax abuse/misuse when used with and without other substances reported by the American Association of Poison Control Centers

Body system / Event	Cases reported	Relationship to exposuure	
		Related	Unknown
None	8 cases	0	0
Any	9 cases	21 of 24	3 0f 4
Gastrointestinal			
Abdominal pain	4	4	0
Diarrhea	2	2	0
Melena	1	1	0
Nausea	1	1	0
Vomiting	3	3	0
Neurological			
Ataxia	2	2	0
Coma	1	1	0
Confusion	2	1	1
Dizzy / vertigo	1	1	0
Drowsy / lethargic	2	1	1
Seizure – multiple	1	0	1
Ocular			
Mydriasis	1	1	0
Non-reactive	1	1	0
Miscellaneous			
Hypoglycemia	1	1	0
Other	1	1	0
Total	24	21	3

Nine subjects underwent decontamination treatments including charcoal and irrigation. Three subjects received intravenous hydration. One intentional – suspected suicide case received the following eight therapies: decontamination with charcoal, antihistamine, benzodiazepines, IV fluids, intubation, naloxone, oxygen, and ventilation. One case required hemodialysis. Three cases required admission to a critical care unit and three cases required admission to a non-critical care unit. These cases occurred in individuals who ingested other substances along with MiraLax. Among the six cases where MiraLax appeared to be the only exposure agent, the exposure resulted in no clinical effects. The majority of clinical effects experienced by exposed individuals was gastrointestinal in nature; however, the most clinically concerning effects were neurological.

Two subjects enrolled in the clinical trials had a medical history significant for anorexia or bulemia. Both subjects were considered recovered. These subjects did not demonstrate weight loss or noncompliance with MiraLax during study participation.

7.1.14 Human Reproduction and Pregnancy Data

The prescription label for MiraLax classifies the drug as Pregnancy Category C. The label states that animal reproductive studies have not been conducted with MiraLax and that a pregnant woman should not use MiraLax unless the clinical benefit outweighs this risk.

In his review, pharmacologist Tamal Chakraborti, Ph.D. stated that PEG 3350 has been evaluated for tertility and reproductive performance, teratology, and perinatal and postnatal deveopment. Oral reproductive toxicity studies did not reveal any significant adverse effects on reproductive parameters in male or female rabbits and rats. PEG 3350 was not teratogenic at the tested doses and did not affect prenatal and postnatal rat development at doses up to 2 g/kg/day.

This reviewer was unable to find information about whether PEG is actively secreted into and/or concentrated in breast milk. Maternal serum levels of PEG 3350 should be very low based on the pharmacokinetic data presented in this application.

The sponsor proposed label for MiraLax OTC states:

The following pregnancy/breastfeeding warning language is required by 21 CFR 201.62 for OTC Monograph drug products (unless exempt):

> ***If pregnant or breastfeeding**, ask a health professional before use.*

The standard monograph warning is consistent with the labeling language in the MiraLax prescription label and appropriate based on the negative reproductive studies.

7.1.15 Assessment of Effect on Growth

This application does not include assessments of growth effect and does not include studies in pediatric subjects.

7.1.16 Overdose Experience

The sponsor states that large overdoses of MiraLax will result in increased stool frequency and volume, and that at very large doses electrolyte depletion is expected to be minimal. During drug development, Braintree found that any electrolytes added to laxative doses of PEG 3350 were completely absorbed by the gastrointestinal tract. Therefore, MiraLax contains only PEG 3350 and does not include electrolytes as do the PEG 3350 containing gastric lavage drug products. However, electrolytes are included in the gastric lavage PEG

products in an attempt to minimize changes in serum elecrolyte levels during the bowel cleansing process.

In 2005, Eric Brodsky, M.D., a medical reviewer in DGP, reviewed serum electrolyte data submitted in the pivotal clinical trials for NuLYTELY. Hyponatremia occurred in 22% of patients who used NuLYTELY prior to colonoscopy and this incidence increased to 31 – 36% when serum sodium levels were checked two to three days following the bowel cleansing. Hypocalcemia occurred in 6 – 12% of subjects using NuLYTELY as a bowel cleanser. Based on this information, it is possible that MiraLax overdose could result in clinically significant electrolyte changes. The FDA Adverse Event Reporting System (AERS) database has reports of new onset seizures associated with clinically significant hyponatremia immediately following bowel cleansing with PEG 3350 plus electrolytes.

As mentioned above, the AAPCC performed a database search and prepared a report on potential cases of MiraLax overdose called in to the Poison Control Centers. They identified 42 possible cases of MiraLax overdose with overdose defined as a dose greater than two times the recommended 17 g daily dose (> 34 g/day). The 17 g dose is the recommended dose for adults; currently there is no pediatric indication or dosing approved by FDA. The case report information on dosing was unclear and nonspecific. Fourteen cases were in adults ages 18 – 85 years. Twenty-three cases were in children: seven infants ages one month to two years and 15 children ages two years to 12 years. Fifteen adult cases and 12 pediatric cases were female.

Twenty-six of the 42 cases reported no clinical effect of the possible overdose. The other 16 cases reported 24 clinical events that occurred after using 51 – 255 g of PEG 3350.[17] Nineteen of these events were gastrointestinal, and 15 were either diarrhea or vomiting. Five events were not gastrointestinal in nature and included: irritability, tremors, and fever. Most cases did not require any treatment. Medical outcomes for all cases were classified as either: no effect, minor effect, or minimal clinical effects possible.

Postmarketing data does not include any reports of overdose. A 2006 safety report on PEG by Ann Corken-Mackey, a safety officer in the Office of Surveillance and Epidemiology, identified AERS reports that suggest off-label use of MiraLax for gastric lavage. Such off-label use technically involves a MiraLax overdose.

The sponsor summarized a case of PEG misuse/overdose in a four year old girl from the published literature. A four year old Hispanic girl presented to the emergency room (ER) two hours after ingesting 24 tablets of 6-mercaptopurine. She was treated at home with ipecac syrup and vomited twice. Physical exam and vital signs were normal in the ER. She was treated with activated charcoal and GoLytely per nasogastric tube was ordered. In error, the girl received 391 mL (23 grams) of PEG plus electrolytes intravenously. The patient recovered without complications, and there were no shifts in clinical chemistry results or blood ethylene glycol levels. She was admitted to the hospital for observation

[17] For comparison, a single bowel cleansing dose of GoLYTELY contains 236 g PEG 3350 and a single bowel cleansing dose of NuLYTELY contains 420 g PEG 3350.

and discharged 36 hours later.[18]

7.1.17 Postmarketing Experience

Since approval, Braintree has distributed [redacted] market units (providing 15 – 30 days of therapy) of MiraLax or PEG 3350 laxative. The sponsor received a total of 125 adverse reaction reports up to the time of NDA submission. The estimated postmarketing adverse reaction rate for PEG 3350 laxative is one adverse reaction per [redacted] units dispensed. Table 33 summarizes the adverse event reports by year and Body System.

Table 33: Post-marketing adverse event summary (February 19, 1999 – August 1, 2005)

Body System	Year of event							
	1999	2000	2001	2002	2003	2004	2005	Total
Allergic reaction	3	7	6	10	14	11	3	54
Gastrointestinal	2	3	3	2	4	17	7	38
Edema	0	0	1	0	0	0	0	1
Brain	0	1	0	0	0	2	1	4
Death	0	0	0	1	0	1	0	2
Miscellaneous	1	3	4	3	4	6	5	26
Total	6	14	14	16	22	37	16	125

Of these 125 reported adverse events, 22 were considered serious adverse events that were reported to FDA as 15-day reports. Nine of these SAEs occurred in individuals under age 18 (eight were age 12 or younger) and therefore involved off-label use. These SAEs included two seizures: one in a 2.5 year old girl using anticonvulsants for a previously diagnosed seizure disorder, and one in a two year old male with a family history (but no personal history) or seizure disorder. In addition, a 17 year old male with bipolar disorder tried to commit suicide while using PEG 3350 laxative. Among adults with SAEs, a 77 year old female experienced hyponatremia and seizures after using MiraLax off-label as a bowel cleansing preparation.

Table 34 provides a summary of all reported postmarketing SAEs associated with the use of PEG 3350 laxative.

[18] Rivera W, Velez LI, Guzman DD, Shepherd G. Unintentional intravenous infusion of Golytely in a 4-year-old girl. Ann Pharmacother. 2004 Jul-Aug; 38(7-8): 1183 – 5.

Table 34: 15-Day postmarketing adverse reaction reports

Report number	Age Gender	Adverse Event	Additional information
990010	M, ? age	Two events of transient hemiparesis	Occurred after initiation of MiraLax therapy
000014	F, 10 yrs	Mouth sore	Taking MiraLax and Bactrim
000015	M, 63 yrs	Left-sided chest pain	History of hypertension. Enrolled in clinical trial. Hospitalized and diagnosed with fractured ribs and bone metastases and renal carcinoma.
000017	M, 26 mths	Right-sided seizure	Family history of seizures
000019	F, 3 yrs	Had an *unexplained reaction*	Hospitalized for extensive testing and psychological evaluation. All testing negative.
010005	F, 27 mths	Hair loss	None
020019	F, 44 yrs	Orange-red tinted urine and decreased urine output	None
020021	F, 82 yrs	Mouth sores	Occurred two weeks after starting MiraLax
020030	F, 92 yrs	Heart failure and death	Occurred two days after using one dose of MiraLax
030021	M, 56 yrs	Bleeding in the penile area upon urination	None
030023	F, 4 yrs	Irritable, lethargic, crying for no apparent reason	None
030030	M, 52 yrs	Anaphylaxis	Used MiraLax off-label as a bowel preparation
030037	F, 77 yrs	Hyponatremia and seizures	Used MiraLax off-label as a bowel preparation
040014	M, 12 yrs	Mouth sores	None
040015	F, 81 yrs	Swollen hands and eyes, muscle pain in right arm, and left flank pain	None
040016	F, 39 yrs	Giant cell arteritis	Considered an allergic reaction
040019	F, 9 yrs	Tic – first in eyes, then generalized to nose and arms	She also noted headaches, loss of focus, cramps, and arrhythmia
040041	F, 39 yrs	Infant developed diarrhea	She was using MiraLax while breastfeeding
040044	M, 54 yrs	Uncontrolled diarrhea and dehydration	Followed two doses of MiraLax
050005	M, 17 yrs	Attempted suicide while using PEG 3350 laxative	Bipolar disorder
050016	F, 2 yrs	Seizures	Using Keppra and Tegretol to treat seizure disorder. Using MiraLax for constipation. Anti-convulsants discontinued and on follow-up patient doing well.
050062	F, 78 yrs	Chronic diarrhea and rash	Hospitalized. Used Glycolax.

Reviewer comments:

Causality can not be determined in many of these cases due to the small number of events, the lack of more specific information, lack of follow-up and rechallenge, and confounding factors such as other medical conditions and medications. However, this reviewer has the following comments:

1. *It is likely that the case of left sided chest pain associated with renal carcinoma*

metastases and the death of a 92 year old woman with heart failure following a single dose of MiraLax are unrelated to the use of MiraLax.

2. *It is interesting to note that among 22 postmarketing report, three individuals reported mouth sores. One of these individuals was using Bactrim and MiraLax concomitantly. Among the adverse events reported by subjects in the clinical trials submitted to this application (851-CR1, 851-CR3, and 851-ZCC), the only similar adverse events were one report of stomatitis, one report of swollen tongue, and one report of gingival pain.*

3. *Episodes of diarrhea following use of MiraLax are most likely related to drug use. With the minimal systemic absorption of MiraLax, it is unclear whether diarrhea in a breastfeeding infant is related to the mother's use of MiraLax.*

4. *The hyponatremia and seizures following use of MiraLax as a bowel preparation are probably related to MiraLax use. The seizures following off-label use of MiraLax in young children could possibly be related to MiraLax use. Even if these two children were predisposed to seizures, an electrolyte shift secondary to MiraLax use theoretically may have altered seizure threshold.*

5. *According to the prescription label, hypersensitivity reactions have occasionally been reported in individuals using PEG. Specific incidences of sources of data are not provided in the label or in the medical officer reviews for NDA 20-698. As stated in section 7.1.10, this reviewer was unable to find any reports of allergic reactions to high molecular weight PEG products in the literature. None of the subjects in the submitted clinical trials discontinued from the study due to an allergic reaction to study drug. The actual Medwatch forms for the 15 postmarketing adverse events have been requested from the sponsor.*

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 635 subjects were exposed to MiraLax in the three clinical studies conducted to support this prescription-to-OTC switch application. One hundred twenty of 635 subjects enrolled in a one month study; 204 enrolled in a six month study; and 311 enrolled in a 12 month study. Table 1 in section 4.2 summarizes the clinical studies performed during the drug development program. The table includes general information about study types and numbers of enrolled subjects. Table 35 below presents more detailed information about the

patient pools for the safety and efficacy trials submitted to this application.

7.2.1.1 Study type and design/patient enumeration

Table 35 summarizes study type and design and patient enumeration for the three clinical efficacy and/or safety trials.

Table 35: Summary of study type and design and patient enumeration for the three efficacy and/or safety trials

Study	Design	Control	Dose	Subjects				Treatment duration	Safety measures
				Total*	Gender* (M/F)	Age* (mean)	Elderly* (≥ 65 yrs)		
851-CR1	Double-blind Parallel group	Placebo	Miralax 17 g/day Dose reduction allowed	MiraLax: 204 Placebo: 100	46/258	53	75	6 months	AEs Labs
851-CR3	Single arm Open label	None	Miralax 17 g/day Dose reduction allowed	MiraLax: 311	63/248	57	117	12 months	AEs Labs
851-ZCC	Open label Parallel group	Zelnorm	Miralax 17 g/day Zelnorm 6 mg BID Dose reductions allowed	Miralax: 120 Zelnorm: 117	24/213	46	31	1 month	AEs

* Intent-to-treat population

7.2.1.2 Demographics

Table 36 below provides a comparative illustration of the demographic characteristics of the study subjects across the three clinical studies.

Table 36: Comparative Study Demographics for Studies 851-CR1, 851-CR3, and 851-ZCC

Demographic	Study 851-CR1		Study 851-CR3	Study 851-ZCC	
	Placebo	MiraLax	MiraLax	MiraLax	Zelnorm
Age (years)					
N	100	204	311	120	117
Mean (SD)	54.4 (15.0)	53.1 (14.8)	56.9 (16.4)	46.1 (14.4)	46.9 (14.5)
Gender					
Female	83 (83%)	175 (86%)	248 (80%)	109 (91%)	104 (89%)
Male	17 (17%)	29 (14%)	63 (20%)	11 (9%)	13 (11%)
Race					
Caucasian	87 (87%)	168 (82%)	248 (80%)	72 (60%)	79 (68%)
African American	11 (11%)	28 (14%)	49 (16%)	31 (26%)	26 (22%)
Other	1 (1%)	4 (2%)	4 (1%)	5 (4%)	5 (4%)
Missing	1 (1%)	4 (2%)	10 (3%)	12 (10%)	7 (6%)
Ethnicity					
Hispanic	7 (7%)	12 (6 %)	Not	18 (15%)	13 (11%)
Non-Hispanic	93 (93%)	1992 (94%)	provided	102 (85%)	103 (88%)
Missing	0	0		0	1 (1%)
Weight (kg) Mean (SD)	75.1 (15.6)	74.4 (16.3)	77.3 (17.6)	77.0 (22.4)	75.8 (18.3)
Constipation Hx (yrs) Mean (SD)	22.6 (19.2)	23.4 (18.7)	17.9 (19.1)	16.2 (14.2)	18.9 (18.2)

For the two studies without upper age restrictions, the mean age of study subjects was between 53 and 57 years of age with age ranges of 20 – 92 years in Study 851-CR1 and 19 – 95 years in Study 851-CR3. The age range of subjects in Study 851-ZCC was 19 – 81 years; however, part way through enrollment, the protocol was amended to exclude females under age 65 years and all males. As predicted, the mean age of study subjects and the percentage of the study population that is male are lower in 851-ZCC than in the other two studies. Relative to the American population as a whole, African Americans were well represented in the study populations. In the 851-ZCC population, African Americans and those of Hispanic ethnicity comprised a relatively higher proportion of the study population compared to the other studies. These differences may have been related to study center number and diversity (851-ZCC enrolled at 25 centers whereas the other two studies enrolled at 50 centers) or to other factors not readily identifiable through data review.

Study subjects had a mean constipation history of 16.2 – 23.4 years with wide standard deviations up to ±19.2 years.

There were no statistically significant differences between treatment groups at baseline.

Reviewer comment:

Occasional constipation and even constipation itself can be difficult to define given the wide variability in bowel habits among individuals within one culture let along across cultures. However, it is important to note that study subjects enrolled in these studies had lengthy constipation histories. At a minimum, they had constipation histories of one year. At a maximum, subjects had constipation histories of more than 40 years. This reviewer notes that NDA 22-015, currently under review, is for the use of MiraLax OTC for the treatment of occasional constipation. It is not clear whether the safety profile for MiraLax use in subjects with chronic constipation is the same or different from that of OTC consumers who experience constipation only occasionally. Conversely, it is not well established whether consumers who use OTC laxatives for the treatment of occasional constipation actually have occasional constipation or whether they have chronic constipation that they treat occasionally with laxatives.

7.2.1.3 Extent of exposure (dose/duration)

Table 37 illustrates subject compliance with the assigned study drug during the respective studies. Given that each of the three clinical studies lasted a different length of time, the duration of each study is also included in the table. Duration of the study would be expected to influence overall subject compliance with therapy as well as the contribution to overall subject exposure to the proposed drug product.

Table 37: Study Medication Treatment Compliance

	851-CR1		851-CR3	851-ZCC	
	Placebo (n= 100)	MiraLax (n = 204)	MiraLax (n = 311)	MiraLax (n = 120)	Zelnorm (n = 117)
Study duration	6 mths	6 mths	12 mths	1 mth	1 mth
Mean%	86.3%	88.9%	72.9%	94%	91%
SD	18.4%	17.9%	23.9%	*	*
Interim compliance % (SD) 2 mths 6 mths 9 mths 12 mths	-	-	76.5% (25.6) 79.7% (23.7) 80.0% (23.2) 71.2% (29.0)	-	-

* The sponsor did not provide standard deviations but stated that 8 (7%) MiraLax subjects and 18 (15%) Zelnorm subjects had compliance levels of <80%.

Compliance with study treatment was lower for subjects in Study 851-CR3 throughout the study compared to the other two studies. Subjects were more compliant with study medication in the one month open-label, active comparator trial (851-ZCC) than in the six month randomized, placebo-controlled trial (851-CR1). Interestingly, the compliance rates for the two different treatment groups within each comparative study were similar whether the treatment arm was a placebo or an active treatment.

Study subjects using MiraLax in Studies 851-CR1, 851-CR3, and 851-ZCC provided over 300 patient years of MiraLax exposure at the labeled dose. Table 38 illustrates more detailed information about extent of MiraLax exposure in each of these three studies.

Table 38: Extent of MiraLax Exposure

Measure	Study 851-CR1 (6 month study)		Study 851-CR3 (12 month study)	Study 851-ZCC (1 month study)	
	Placebo	**MiraLax**	**MiraLax**	**MiraLax**	**Zelnorm**
Total dose (g)					
# subjects	93	201	311	113	111
Mean dose (g)	1849.3	2163.3	3677.2	446.5	306.7
SD	1170.2	1069.6	2069.3	89.7	82.1
Mean doses per person (labeled dose)	109	127	216	26	51 (dosed bid)
Total Weeks					
# subjects	100	204	311	113	112
Mean weeks	15.4	19.5	36.4	3.9	3.8
SD	10.1	9.1	20.0	0.7	0.9
Exposure (patient years)	-	75	218	8	-

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary clinical data sources used for evaluation of drug safety are discussed below.

7.2.2.1 Other studies

This reviewer attempted to review the safety data from the clinical trials submitted in support of NDA 20-698 for prescription Miralax, as these studies were directly relevant to use of Miralax for the treatment of occasional constipation in the nonprescription setting. The medical officer and medical team leader reviews were examined as well as safety summaries submitted by the sponsor upon request.

In NDA 20-698, safety data sources included preclinical (pharmacokinetic?) studies, two pivotal clinical trials, and two supportive clinical trials. For all controlled clinical trials, a total of 286 constipated subjects took MiraLax daily for up to 20 days. An additional 131 subjects took study drug through an open-label study (851-4a), and seven of these subjects used MiraLax daily for 5 years or longer. Overall, these studies provided more that 200 patient years of daily exposure.

In the controlled clinical trials, subjects reported fourteen *unexpected* adverse events, six of which were serious. All fourteen AEs occurred in subjects from the nursing home population. The SAEs included one death, one CVA, and one MI and were associated with subjects' pre-existing medical conditions. Other *unexpected* AEs included: abdominal pain and/or cramping (two subjects who withdrew from studies), heartburn and nausea (1 subject), urinary tract infection (1 subject), severe headache (1 subject), elevated liver function tests (two subjects – both withdrawn), muscle aches (1 subject), dislocated shoulder (1 subject), and syncope and volume depletion (1 subject). The investigators described all of these events as unrelated to study medication and due to pre-existing conditions.

Expected adverse events from the four controlled studies included the following gastrointestinal (GI) events: 30 reports of diarrhea, 42 reports of impaction or constipation (38 were from study 851-4 which was conducted in nursing home subjects), nine reports of nausea, three reports of abdominal cramping, and one report each for abdominal bloating and rectal irritation. Nineteen of 30 subjects who experienced diarrhea discontinued the study medication – 6 while using 17 g/day MiraLax and 15 while using 34 g/day or Miralax. The number of discontinuing subjects adds up to more than thirty due to some subjects stopping more than one treatment during the crossover study. In study 851-4, subjects were treated with reduced doses of MiraLax (6 or 12 g) because four of the first five subjects enrolled experienced diarrhea at the 17 g and 34 g doses. During the MiraLax treatment periods, seven subjects experienced constipation while using MiraLax 12 mg/day. Eight subjects had constipation while using MiraLax 6 g/day, and an additional two subjects were impacted.

Among subjects enrolled in Studies 851-3, 851-4, 851-5, and 851-6, twenty-four of 161 subjects were ages 65 years and older. Three of 24 elderly subjects and nine of 137 younger subjects experienced diarrhea. Two of the three elderly subjects who experienced diarrhea were nursing home patients from Study 851-4. Elderly individuals from nursing homes used reduced daily doses of MiraLax (6 or 12 mg/day) if they experienced diarrhea using 17 g/day of MiraLax. There were no reports of diarrhea or loose stools associated with the six and twelve gram doses of PEG 3350 but effective relief of constipation was not always achieved.

Reviewer comment:

1. *The data from study 815-4 conducted in a nursing home population suggests*

debilitated elderly subjects are more likely to experience diarrhea at the 17 g/day dose of MiraLax but are also more likely to experience constipation and stool impaction at reduced doses.

2. *Otherwise, the adverse event data available from the studies used to support NDA 20-698 appear similar to those obtained from the three clinical studies submitted to support the application currently under review.*

7.2.2.2 Postmarketing experience

All available postmarketing safety information was presented in section 7.1.17.

7.2.2.3 Literature

The sponsor submitted 32 literature articles for review. Seven of these articles include data relevant to the safety review for MiraLax. Data from these articles are summarized below.

Bouhnik Y, Neut C, Raskine L, Riottot M, Guillemot F et al. Prospective, randomized, parallel-group trial to evaluate the effects of lactulose and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation. Aliment Pharmacol Ther. 2004; 19: 1 – 11.

Sixty-five patients with chronic idiopathic constipation participated in this controlled, multi-center, randomized, parallel-group study. Participants were randomized to four weeks of treatment with either lactulose or PEG 4000 at a dose of 20 g/day for the first week. After the first week of treatment, dose adjustments from 10 – 30 g/day were allowed based on efficacy and tolerance. During the last two weeks of the study, the dose of study drug was maintained at the same level. Stools were recovered for bacteriological analysis at study days 1, 21, and 28.

Participants used a daily diary card to record the number of stools and the severity of the following symptoms: flatus, bloating, borborygmi, and abdominal pain. Symptoms were rated on a four point scale from zero (symptom absent) to three (symptom severe).

In the last week of the study, PEG treated subjects presented soft or liquid stools 60% of the time. Lactulose treated subjects presented normal stools 42% of the time. After 28 days of treatment, 71% of PEG treated subjects had more than three stools per week. There were no severe adverse events. Among PEG treated subjects, the following percentages of subjects experienced at least one day of the following symptoms with moderate to severe intensity:

- Borborygmi: Week 1 (52%), Week 4 (39%)
- Bloating: Week 1 (74%), Week 4 (43%)
- Abdominal pain: Week 1 (61%), Week 4 (26%)
- Excessive flatus: Week 1 (74%), Week 4 (65%).

Lactulose induced significant changes in the composition of fecal flora with increases in bifidobacteria counts. PEG inhibited most of the metabolic activities of the fecal flora, and this was evidenced by decreases in total short-chain fatty acids, butyrate, acetate, and fecal bacterial mass. PEG did not alter colony counts of *Lactobacillus*, clostridial spores, *Bacteroides* or enterobacteria. The authors state that maintenance of the bacterial fermentation process in the colon is important for health. Short chain fatty acids, especially butyrate, are important for the energy metabolism and normal development of colonic epithelial cells and are thought to play a protective role in the colon. The long term effects of decreased fatty acid production, such as that observed with PEG therapy, are unknown. The authors concluded that PEG inhibits the colonic fermentation process usually considered beneficial to the host.

Reviewer comment:

This finding raises a theoretical concern with long term or frequent repeated use of PEG by consumers. However, at this time, no colonic epithelial changes have been related to PEG 3350 use in humans. This reviewer has not been able to locate animal studies evaluating the effects of chronic PEG 3350 treatment on colonic mucosa.

This theoretical concern is related to chronic use and should not be a safety issue for this product when used as directed. The sponsor proposes [redacted] *duration of use for MiraLax OTC for the treatment of occasional constipation.*

Corazziari E, Badiali D, Bazzocchi G, Bassotti G, Roselli P et al. Long term efficacy, safety, and tolerability of low daily doses of isoosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. Gut 2000; 46: 522 – 526.

This was a multicenter, double-blind, placebo-controlled, parallel group study to assess the long term effectiveness, safety, and tolerability of low daily doses of iso-osmotic PEG electrolyte solutions. Patients were recruited from a population seeking medical advice for chronic constipation and were followed over 24 weeks. Inclusion criteria included: ages 18 – 75 years and chronic constipation as defined by the Rome diagnostic criteria:

- Less than two bowel movements per week for at least 12 months or
- the presence of two or more of the following in at least 25% of BM's (when laxatives and/or enemas are not used):
  - straining
  - sense of incomplete evacuation
  - hard stools.

Eligible subjects had negative screening tests for organic disorders of the digestive tract, no anorectal disorders, no abnormalities on barium enema or colonoscopy; and normal laboratory tests including thyroid function tests. Individuals with the following conditions and using the following medications were excluded: inflammatory bowel disease; previous GI tract surgery; chronic use of GI motility drugs; chronic systemic, metabolic, neurological, and psychiatric illnesses.

During the four week run-in period, all 70 subjects used 14.6 g of a PEG solution with electrolytes (PMF-100) BID. In addition, study staff instructed subjects to standardize their diets and include a mean daily intake of 15 g fiber and 1500 mL water daily. Subjects were asked to avoid use of laxatives, rectal evacuants, and enemas. Subjects were allowed to reduce their dose of study drug to once daily administration based on BM frequency. Subjects who responded to therapy and no longer met the Rome criteria for constipation were randomized to 20 weeks of treatment with either PEG 14.6 g BID or a matched maltodextrin placebo BID.

During the study, no other medications were allowed. Rescue laxatives were used only if subjects had no BM for at least five consecutive days. Subjects used weekly diary cards to record drug taken, number of BMs, stool consistency, straining at defecation, and use of laxatives or enemas. They recorded the following symptoms: abdominal pain, abdominal bloating, flatulence, and borborygmi. In addition, the physician asked about abdominal symptoms at study visits. At study visits 2, 3, 4, 5, 6, and 7, subjects returned completed diary cards and unused study medicine. At study visits 1, 4, and 7, subjects had a physical exam with vital sign assessments and blood draws for complete blood count, sodium, potassium, creatinine, glucose, transaminases, alkaline phosphatase, and BUN. Baseline calcium, phosphorus, and sedimentation rate were measured at Visit 1.

Normal BM frequency was defined as at least three BMs per week. A treatment success was defined as complete remission of constipation with three or more BMs per week, no use of laxatives, no straining with defecation, feeling of complete evacuation, and no hard/pellety stools. There was a high number of dropouts in the placebo group after the first eight weeks of the study, so data were analyzed for the entire treatment period and for the first eight week period (to visit 4).

Seventy subjects entered the study, 12 men and 58 women between the ages of 18 and 73 years and a mean age of 43 years. Thirty-three subjects randomized to the PMF-100 group and 37 to the placebo treated group. At the end of the run-in period, there were no significant differences between the treatment groups with regard to stool frequency, straining at defecation, stool consistency, or use of laxatives. Of the 33 subjects assigned to the PMF-100 group, 32 completed the first eight week study period and 23 completed the entire study. Of the 37 subjects assigned to the placebo group, 33 completed the first eight week study period, but only 15 subjects (30%) completed the entire study. Lack of treatment response was the reason for early discontinuation in 7% of PMF treated subjects and 46% of placebo treated subjects.

At the end of the study, 77% of the PMF treated subjects and 20% of the placebo treated subjects were asymptomatic for constipation. In the placebo treated group, mean BM frequency decreased from 7.7 BMs per week at visit 2 at the end of the run-in period (with PMF treatment) to 4.3 BMs per week at visit 4 (study week eight). From visit 4 to visit 7, BM frequency did not change significantly, but many subjects discontinued the study early. Use of additional laxatives among PMF treated subjects progressively decreased during the duration of the study but progressively increased among placebo treated subjects.

Abdominal pain, flatulence, and borborygmi progressively decreased in the PMF treated group and did not change substantially in the placebo treated group. Abdominal bloating was less severe and occurred less often in PMF treated subjects compared to placebo treated subjects. The occurrence of gastrointestinal (GI) symptoms and non-GI symptoms were not statistically different between treatment groups. Among PMF treated subjects, adverse events led to study withdrawal in two subjects: one had abdominal bloating; one had an anal fissure. Vital signs and laboratory values were within normal limits at visit 1 and did not vary significantly across the duration of the study or between study treatment groups.

Reviewer comments:

1. *Results from this study demonstrate that after four weeks of daily laxative treatment and complete resolution of constipation symptoms in most subjects, constipation symptoms recur following laxative discontinuation. Laxative use progressively increased in the placebo treated group following randomization.*

2. *While the numbers were not statistically significant, this reviewer notes that during this study, the following adverse events were reported numerically more often by subjects using PMF:*
    - *Nausea (22 vs. 17)*
    - *Anal pain (5 vs. 0)*
    - *Hematochezia (7 vs. 2)*
    - *Fecal incontinence (3 vs. 0).*

3. *The results of this study are consistent with the original clinical data submitted in support of this application, and suggest no new safety signals.*

Di Palma JA, MacRae DH, Reichelderfer M, Hamilton JW, Cleveland MvB. Braintree polyethylene glycol (PEG) laxative for ambulatory and long-term care facility constipation patients: Report of randomized, cross-over trials. Online Journal of Digestive Health 1999; www.ojdh.org.

This article reported results on two randomized, double-blind, placebo-controlled crossover trials performed to determine the safety and efficacy of MiraLax laxative in two different study populations. Study subject candidates for each study were eligible for enrollment if they demonstrated the following during a seven day qualifying run-in period: three or few bowel movements per week or ≤ 300 g stool per week. One study site enrolled healthy

adults with constipation. The other site enrolled long term care patients with special needs from stroke or medical debility. Study candidates were excluded for: prior GI surgery; known or suspected GI obstruction; ileus; heart failure; renal failure; ascites; other known chronic bowel, liver, renal or cardiopulmonary disorders; pregnancy or lactation; weight less than 100 pounds.

Subjects who met enrollment criteria were randomized to one of three 10-day treatment schedules chosen according to a random numbers table. Based on concerns about patient compliance, the randomization scheme did not assign any subjects to placebo treatment during the first treatment period. Every subject used each of the following study treatments during one of the treatment periods:

- 17 g/day PEG 3350
- 34 g/day PEG 3350
- Placebo.

Subjects drank 250 mL once daily, preferable in the morning. The solution was premixed in a four liter bottle for the healthy adult population, whereas the dose was prepared daily for the long term care patients by facility staff. Subjects used diary sheets to record each BM and associated subjective symptoms. They rated stool consistency, ease of passage, cramps, and flatus. All stools were collected and weighed. Subjects who used a non-study laxative or an enema during the treatment period were scored and analyzed as treatment failures. Subjects could discontinue treatment for lack of efficacy or diarrhea but were allowed to start the next treatment phase. After each 10-day treatment period, study investigators collected blood and urine samples for CBC, blood chemistries, and urinalysis.

The authors presented safety and efficacy results for both study populations: healthy adults, constipated (AC) and long term care patients (LT). Fifty AC subjects (47 female, 3 male) completed the protocol, and 35 LT subjects (19 females, 16 male) completed the protocol.

AC population:
Compared to placebo, PEG 3350 produced a dose-related significant increase in BM frequency and stool weight. The 17 g/day dose of PEG was significantly better than placebo and the 34 g/day dose was significantly better than the 17 g/day dose and placebo. Subjects reported a total of 13 episodes of diarrhea while using 34 g/day PEG 3350 and 5 episodes of diarrhea while using 17 g/day PEG 3350. One subject reported diarrhea while using placebo; however, there were carry-over effects from one treatment to the next as there were no washout periods between treatments. In these studies, all placebo treatment periods followed ten or twenty days of PEG 3350 use. The authors stated:

> *Some carry-over effect was observed in the crossover analyses from [the] 34 g dose treatment into placebo treatment. This effect was ignored as it would only tend to obscure conclusions of efficacy.*

LT population:

Seventeen patients completed the study, and there was no significant difference between treatment groups for BM frequency and stool weight. The authors did not provide information on episodes of diarrhea or other GI adverse events often associated with laxative use. They reported one death of a terminally ill subject, one myocardial infarction, one cerebrovascular accident, one "sore stomach", and one episode of severe nausea associated with metastatic neoplasia. The investigators classified all of these events as unrelated to study treatment.

There were no clinically significant changes in laboratory measurements for subjects studied at either site.

Reviewer comments:

- *It is important to note that the 1999 and 2000 Di Palma et al articles acknowledge Jack Di Palma, MD, as the medical director/consultant and co-author, Mark Cleveland, Ph.D., as the Vice President of New Drug Development for Braintree Laboratories, Inc., the sponsor of this application.*

- *The design and outcomes of these studies are identical to two studies submitted as one pivotal and one supportive study to NDA 20-698, prescription MiraLax. The study conducted in the healthy adult population is study 851-3. This study's design flaws resulted in FDA requesting further data analyses based solely on the placebo run-in period and first randomized treatment period to compensate for the lack of washout between randomized treatment periods. Ultimately, FDA concluded that the reanalyzed data supported safety and efficacy of MiraLax 17 g/day based on a 10 day treatment design.*

  The study conducted in the long term care population is study 851-4. Four of the first five subjects enrolled in this study developed diarrhea on either 17 g/day or 34 g/day of PEG 3350. The PEG doses for the remaining 30 subjects were reduced to 6 g/day and 12 g/day. The author did not mention this in the article when presenting the study results.

- *The incidence of diarrhea and lack of clinically significant changes in laboratory assessments in the healthy adult population is similar to results seen in studies submitted in support of the current application.*

Di Palma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MvB. A randomized placebo-controlled, multicenter study of the safety and efficacy of Braintree polyethylene glycol laxative. Am J Gastroenterol. 2000; 95: 446 – 50.

This study was a randomized, double-blind, placebo-controlled, parallel group, multicenter study designed to evaluate the safety and efficacy of PEG 3350, MiraLax, in constipated, otherwise healthy adult outpatients. Subjects were enrolled who had two or fewer stools during a seven day qualification period. During the qualification period, subjects used a diary to record all BMs. Subjects were excluded for: allergy or sensitivity to PEG; prior

GI surgery; known or suspected GI obstruction; ileus; heart failure; renal failure; ascites; other known chronic bowel, liver, renal or cardiopulmonary disorders; pregnancy or lactation; or weight less than 100 pounds. Study investigators recruited subjects from four gastroenterology practices and through local advertising.

Enrolled subjects were randomly assigned to treatment with either 17 g/day PEG 3350 or 17 g/day placebo (dextrose powder) according to a random numbers table. The author stated that unpublished studies established 17 g/day PEG 3350 as the minimum effective dose. Subjects each received a polyethylene jar containing 255 g study drug material and a plastic scoop that delivered the appropriate dose. Subjects mixed a single scoop of study drug in eight ounces of beverage and drank it each day.

Subjects used diary sheets to record each BM and associated subjective symptoms rating stool consistency, ease of passage, cramps, and flatus. Subjects who withdrew from the study due to a perceived lack of efficacy or diarrhea and subjects who self-treated with a different laxative or an enema were scored and analyzed as treatment failures. Study investigators collected blood and urine samples at baseline and at the end of the 14-day treatment period for CBC, blood chemistries, and urinalysis.

A total of 151 adults were randomized including 131 women and 20 men. Thirteen men and 67 women were randomized to PEG and seven men and 64 women to placebo. Investigators excluded seven subjects from analysis due to a baseline laboratory abnormality or noncompliance with the study protocol. The efficacy analysis was based on 141 subjects, and 135 completed the protocol. The safety population included all enrolled subjects. The study protocol defined an effective treatment (treatment success) as more than three BMs per seven day period. A treatment failure was less than three bowel movements per seven day period, use of laxatives or enemas, or early withdrawal.

During the pretreatment qualification week, there were no differences seen between treatment groups with regard to stool consistency, difficulty of passage, or symptoms of severe cramping or gas. During the treatment phase, PEG treatment was statistically more effective than placebo for relief of constipation whether data analysis was based on the first week of treatment alone, the second week of treatment alone, or both weeks of treatment combined. On average, by week two, PEG treated subjects had 4.5 BMs weekly whereas placebo treated subjects had 2.7 BMs weekly. Significantly fewer PEG treated subjects reported hard stool consistency, difficult stool passage, cramping, or gas compared to placebo treated subjects. Evaluation of adverse event data and laboratory measurements revealed no statistically or clinically significant differences between treatment groups. The authors did not describe adverse events experienced during the trial.

In the discussion section, the authors comment that use of saline laxatives (magnesium and phosphate salts) is associated with significant absorption of the component ions, which can result in systemic toxicity including dehydration and electrolyte abnormalities including potassium and calcium depletion. They comment that this presents an acute problem for renal and heart patients and that labeling for these products cautions against use in these populations. They state that PEG 3350 laxative does not affect patient electrolytes or

serum osmolarity.

Reviewer comments:

1. *The study presented in this article is Braintree study 851-6, which was submitted as the second pivotal study in support of NDA 20-698, prescription MiraLax. The authors state that PEG demonstrated statistical superiority over placebo at one week of treatment and at two weeks of treatment. The medical officer and medical team leader reviews of this study from NDA 20-698 state that upon FDA statistical analysis, the study supported efficacy only after the first week of treatment.*

2. *The authors comment on the labeling cautioning use of saline laxatives in persons with cardiac and renal disease due to the potential for dehydration and electrolyte abnormalities. Laboratory data submitted to this application from study 851-CR1 and 851-CR3 suggest that serum phosphate levels increase with chronic MiraLax use. This effect may not be seen with short courses of therapy (7 to 14 days) unless treatments are frequently repeated. In addition, despite the authors' suggestion that PEG would be safe (or safer) to use in cardiac and renal patients, compared to the saline laxatives, cardiac and renal patients were excluded from enrollment in both this study and the other pivotal study that supported MiraLax approval. Despite a lack of study data in individuals with cardiac and renal disease, the prescription label for MiraLax does not warn against use or suggest use with caution in patients with cardiac and/or renal disease. The clinical trials section of the label does not note that these populations were not studied.*

Di Palma JA, Smith JR, Cleveland MvB. Overnight efficacy of polyethylene glycol laxative. Am J Gastroenterol. 2002; 97: 1776 – 1779.

The purpose of this randomized, double-blind, parallel group pilot study was to determine an optimal single dose of PEG 3350 for relief of constipation within 24 hours. Twenty four adult subjects were enrolled who met Rome II criteria for constipation:

- Satisfactory stools less than three times weekly
- Met one of the following criteria with more than 25% of defecations for 12 weeks during the preceding 12 months:
    - Straining
    - Lumpy or hard stools
    - Sensation of incomplete evacuation
    - Sensation of anorectal obstruction/blockage
    - Need for manual maneuvers to facilitate passage of stool.

Subjects were excluded for: meeting criteria for irritable bowel syndrome; pregnancy or breastfeeding; occult blood in the stool not previously evaluated; known or suspected bowel perforation; bowel obstruction; fecal impaction; gastric retention; inflammatory bowel disease; history of bowel resection or colostomy; using medications known to cause constipation; allergy to PEG.

Subjects underwent a baseline medical history and physical examination and provided blood samples for blood glucose, serum electrolytes, BUN, creatinine, calcium, and serum osmolality. Stool occult blood testing was done at exam.

Subjects were randomized to one of the following treatments according to a random numbers table:

- 51 g PEG 3350
- 68 g PEG 3350
- 85 g PEG 3350
- Placebo.

Each study treatment was administered as a pre-mixed solution of 250 mL of Crystal Light at the baseline visit. Study subjects received diary sheets to record each BM and associated symptoms. They rated stool consistency, straining, gas, and cramps using a 10-cm line visual analogue scale. Use of alternative laxatives or enemas was not allowed during the study and would result in discontinuation from the study. Diarrhea, defined as more than three large watery BMs, was considered a treatment success and an unexpected adverse event. No BM within two days of dosing with study drug was a treatment failure. Laboratory testing was repeated after the 72 hour observation period. The primary efficacy variable was frequency of BM compared across doses. Safety analysis was based on all subjects who received study treatment and included abdominal pain, flatus, other adverse events, and laboratory evaluation.

Twenty-four subjects (23 women and 1 man) were randomized. Study groups were similar for age, weight, and gender. Nineteen subjects were Caucasian; three were African American; and two were Hispanic. All subject completed the protocol.

All three PEG doses were statistically more effective in producing bowel movements within 24 hours than placebo, and the 68 g dose was the most effective with an average time to first BM of 14.8 hours and to second BM at 19.2 hours. Fifty percent of subjects experienced complete evaluation with the first BM, and 100% with the second BM. Table 39 summarizes the outcomes for all treatment groups.

Table 39: Efficacy comparisons for single dose PEG treatments

Efficacy parameter	Placebo (N = 6)	51 g PEG (N = 6)	68 g PEG (N = 6)	85 g PEG (N = 6)
Time to first BM (h) SD	27.3 (23.1)	11.4 (12.3)	14.8 (9.1)	6.3 (7.7)
Time to second BM (H) SD	47.2 (17.7)	19.6 (14.3)	19.2 (11.3)	10.2 (10.2)
Complete evacuation 1st BM 2nd BM	 0% 60%	 17% 67%	 50% 100%	 50% 60%
Satisfactory BM 1st BM 2nd BM	 50% 60%	 40% 80%	 83% 100%	 50% 100%
Average BMs / 24 h	0.5	2.2	2.2	4.2
Subjects with BM within 24 h	3	5	5	6

There were no reported adverse reactions and no reports of fecal incontinence.

Reviewer comments:

1. *The objective of this study was to produce constipation relief in 24 hours and the primary efficacy variable was BM frequency. By these measures, the 85 g PPEG treatment group was most successful.*

2. *This study raises an interesting question about the most effective way to occasionally treat constipation with PEG 3350 in the nonprescription and prescription environments. The current application proposes [redacted] course of therapy with a daily recommended dose of 17 g/day of PEG 3350. The 51 g and 68 g single dose treatments in this pilot study performed similarly considering that each treatment arm contained only six subjects per treatment arm. The 51 g dose is the equivalent of four 17 g daily doses, and the 68 g dose is the equivalent of five daily doses of PEG 3350. Ideally, future studies should compare the safety and efficacy profiles of PEG 17 g per day for 7 days [redacted] with a single daily treatment of 51 g and 68 g in a population that uses laxatives occasionally to treat constipation.*

3. *This study does not raise any new safety concerns for this application.*

Ragueneau I, Poirier JM, Radembino N, Sao AB, Funck-Brentano C, Jaillon P. Pharmacokinetic and pharmacodynamic drug interactions between digoxin and macrogol 4000, a laxative polymer, in healthy volunteers. Br J Clin Pharmacol. 1999; 48(3): 453 – 6.

This was an open-label, randomized, two-way cross-over study in 18 healthy adult volunteers who received a single oral dose of digoxin 0.5 mg administered alone or in combination with macrogol 4000, 20 g/day over eight days. Coadministration of macrogol 4000 (PEG 4000) with digoxin resulted in a 30% decrease of digoxin AUC and a 40% decrease in digoxin C_{max}. Digoxin t_{max} and half life were not significantly altered by co-administration with macrogol 4000.

The possible implications of these findings are discussed in section 7.4.2.5.

Tran LC, Di Palma. Lack of lasting effectiveness of PEG 3350 laxative treatment of constipation.

Ambulatory males and females ages 19 years and older who reported a history of constipation were candidates for study participation. Individuals who met the Rome II-based constipation criteria for at least 12 weeks during the preceding 12 months could enroll. The constipation criteria included: a satisfactory BM less than three times per week and the following symptoms in more than 25% of defecations: straining, lumpy or hard

stools, the sensation of incomplete evacuation, the sensation of anorectal obstruction/ blockage, and the need for manual maneuvers to facilitate defecation. Individuals who met criteria for irritable bowel syndrome were excluded.

Forty-two healthy females and eight healthy males comprised the study group. Mean age was 52 years, and mean symptom duration was 22.6 months. Four subjects discontinued early: two for use of enemas or laxatives and two for "gas." All four were counted as treatment failures. Mean time to first BM was 44.1 hours (± 47.3 hours). At the end of the 14 day treatment period, 83% of subjects had more than three bowel movements during the last seven days of the study and no longer met Rome criteria for constipation. At a mean of 38 days after active MiraLax treatment ended, 62% (29 of 47 subjects) reported that they used a laxative during the interval between the end of MiraLax treatment and the follow-up interview.

Adverse events experienced by subjects during the study included: constipation, headache, chest congestion, increased blood pressure, and gas.

Reviewer comment:

> *The subjects enrolled in this study had a constipation history that averaged approximately two years. Following the 14-day course of therapy recommended in the prescription MiraLax label, two thirds of subjects needed to treat their constipation symptoms with a laxative again within 30 days. This is important information, because it suggests that consumers who respond to OTC MiraLax may need to repeat their course of therapy more than once a month. Currently, the proposed OTC label does not limit the frequency with which a consumer may repeat the course of treatment and does not suggest a frequency of laxative use or recurrent constipation symptoms that should trigger evaluation by a healthcare provider.*

[redacted]

Overall, these articles provide data that are consistent with the supportive of the clinical data submitted to this application for review. The article by Ragueneau et al raises concerns MiraLax use may affect the absorption of other concomitantly used medications. This could be clinically significant for drugs with narrow therapeutic indices, and this issue needs to be addressed in the MiraLax OTC label.

7.2.3 Adequacy of Overall Clinical Experience

The combination of clinical trial safety data with durations of daily use of six to 12 months and postmarketing experience with more than 26 million market units sold is adequate to support the safe use of Miralax laxative in the nonprescription setting for up to 14 days. Given that four placebo controlled clinical trials were submitted to support safety and efficacy of MiraLax in the prescription setting for the same indication, it is appropriate that the sponsor submitted one placebo-controlled, double blind study and supplemented the safety data with a long term safety study. Most adverse events involve the GI system and are predominantly signs and symptoms associated with constipation and/or laxative use to treat constipation.

Exclusion criteria for the clinical trials were extensive; however, subjects with diabetes, renal impairment, and cardiac disease were included in the studies. It appears that while abnormal thyroid function was an exclusion criterion, individuals with thyroid disorders were allowed to enroll if their thyroid function tests were normal at the time of enrollment. Individuals on a wide variety of medicines that affect bowel function were excluded from study participation. These exclusions will be addressed in labeling with a warning that tells consumers to ask a doctor before use if using other medicines. This language was included in the sponsor's draft label and is also language required in labeling for OTC laxatives marketed under the Monograph. This type of general medicine warning also provides necessary guidance to individuals on narrow therapeutic drugs whose serum drug levels could theoretically affected by concomitant use of MiraLax.

PEG 3350, the active ingredient (and only ingredient) in MiraLax is inert and minimally absorbed systemically. Assessment of QT interval effects is not needed for this drug product.

Reviewer comment:

> *Efficacy data submitted for the prescription approval and efficacy data from the current application support product efficacy at seven days of treatment. To optimize the risk/benefit ratio for MiraLax in the nonprescription setting, this reviewer recommends that the course of treatment be limited to a maximum of seven days. The seven day duration of use would be consistent with that of other currently marketed OTC laxative drug products.*

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pharmacology/toxicology reviewer addresses adequacy of preclinical data in his review.

7.2.5 Adequacy of Routine Clinical Testing

An adequate number of adult, constipated subjects, including a substantial elderly subset

were evaluated in this drug development program. The number of male subjects was significantly smaller than the female subpopulation, but constipation is more common in females and this gender breakdown is typical for constipation/laxative studies. The male subpopulation was large enough to demonstrate similarity to the female subpopulation with regards to adverse event profile. Subjects with higher risk conditions, such as cardiac disease, diabetes, and renal disease, did not exhibit higher incidences of drug treatment related adverse events. Adverse events that did occur with higher frequency appeared to be related to underlying medical conditions.

Subjects with hypothyroidism (clinical and subclinical) and those with IBS were excluded from the clinical studies. These exclusions should be reflected in the OTC label.

The adverse event profile with six to twelve months of MiraLax treatment supports occasional treatment of constipation in an OTC environment with the [redacted] course of therapy. Technically, the clinical studies evaluated drug safety in a chronic constipation population with chronic laxative use. Clinical references, published literature, and the TFM do not provide a definition for *occasional constipation.* If one agrees with descriptions and definitions of constipation in the literature, then idiopathic constipation is a chronic condition that may be treated either occasionally or chronically with laxatives based on the severity of an individual's symptoms. Therefore, it is appropriate to use data in the studied population to support self-treatment in consumers who need to occasionally treat their constipation with a laxative.

Reviewer comment:

Although MiraLax OTC may be safe [redacted]
OTC setting, clinical trial data demonstrate efficacy after seven days of treatment. Therefore, labeled duration of use for this product should be up to seven days.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please refer to the Clinical Pharmacology review for a thorough discussion of the metabolic and clearance data. This reviewer evaluated the sponsor's summaries of studies on the metabolism and clearance of systemically absorbed PEG 3350 and clearance of PEG 3350 from the bowel. These evaluations appear adequate.

No specific drug-drug interactions have been found for PEG; however, some published data suggest that absorption of concomitantly administered drugs may be compromised. This may be clinically important with concomitantly administered drugs that have a narrow therapeutic index, such as digoxin and anti-seizure medications. This reviewer was unable to find any data evaluating how timing of drug administrations influencing this effect. The potential for decreased absorption of NTI drugs should be communicated in the OTC label.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, the clinical data is adequate for approval. However, the application is not complete. The sponsor needs to submit a safety update and more detailed information on the 125 postmarketing adverse event reports has been requested.

7.2.9 Additional Submissions, Including Safety Update

As of August 8, 2006, the sponsor has not submitted a safety update. The sponsor has been notified and will submit the safety update. This information will be evaluated in an addendum to this review at a later date.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As presented in section 7.1.5.5, the most common drug-related adverse events are gastrointestinal in nature. The four GI AEs with the highest incidence among study subjects were:

- Diarrhea
- Loose stools
- Flatulence
- Nausea.

Most of these GI AEs were mild to moderate in intensity. There were no other statistically or clinically significant differences noted in the adverse event profiles for subjects treated with placebo and those treated with MiraLax. A minority of Miralax treated subjects reduced their medicine dose during the study due to GI adverse events. This application proposes use of MiraLax for up to 14 days to treat occasional constipation in the adult OTC population. Rather than instructing consumers how to reduce dose if diarrhea, abdominal cramping, or bloating occurs, the proposed label instructs consumers to stop use in these

situations.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Study 851-CR1 was the only double-blind, placebo-controlled study submitted to support the safety and efficacy of MiraLax OTC for the proposed indication. Therefore, safety data from the placebo and MiraLax treatment arms of this study form the point of reference for comparing adverse event incidences across treatment groups.

7.4.1.1 Pooled data vs. individual study data

The study definition of constipation and enrollment criteria for the three clinical studies were very similar if not identical. Therefore, the adverse event data was sometimes pooled from studies 851-CR1 and 851-CR3. When this was done, data from the separate studies was most often included in the table as well as the combined figures. Due to the short duration of the study and the different population demographics following exclusion of males and elderly subjects, safety data from study 851-ZCC played a more supportive role in the analysis and was not combined with data from the other two studies. These data are reviewed in section 7.1.5 of this review.

No formal statistical testing was performed on the pooled data.

7.4.1.2 Combining data

Data was combined using simple mathematical addition of numerators and denominator to calculate incidences of various adverse events or adverse event groups.

7.4.2 Explorations for Predictive Factors

The sponsor performed data analyses to explore the following patient-predictive factors for adverse drug reactions:

- Duration of Use
- Age
- Race
- Gender
- Occurrence of drug-related diarrhea
- High risk medical conditions
- Use of narrow therapeutic index drugs.

7.4.2.1 Explorations for dose dependency for adverse findings

The sponsor performed dose ranging studies during drug development prior to the approval of MiraLax for prescription marketing. One of the two pivotal studies for NDA 20-698, Study 851-6, randomized subjects to 17 g or 34 g of MiraLax per day. A significantly higher incidence of diarrhea and loose stools occurred at the higher dose. In a trial conducted in elderly patients in nursing homes, four of the first five subjects enrolled experienced diarrhea at the 17 g/day MiraLax dose. Subsequent subjects used 6 – 12 g per day of MiraLax without experiencing diarrhea but with lower rates of efficacy than that seen in trials using 17 g/day of MiraLax.

7.4.2.2 Explorations for time dependency for adverse findings

Study 851-CR3 lasted for 12 months. For the 184 subjects who completed the study, the sponsor compared the incidence of adverse events by MedDRA Body System for the first six months of the study and the second six months of the study to determine whether adverse events incidence increased with duration of use. Table 40 displays the adverse event rates by body system and study segment.

Table 40: Study 851-CR3: Comparison of adverse events that occurred in the first six months and second six months of the study for study completers

Adverse Events	Study Completers[2] (N = 184)	
	First 6 months N (%)	Second 6 months N (%)
Patients with events	131 (71.2)	98 (53.3)
Number of events	238	148
Body system[1]		
Blood/lymphatic	2 (1.1)	1 (0.5)
Cardiac disorders	2 (1.1)	2 (1.1)
Ear/labyrinth	3 (1.6)	2 (1.1)
Endocrine	2 (1.1)	0
Eye	2 (1.1)	3 (1.6)
Gastrointestinal	**57 (31.0)[4]**	**24 (13.0)**
General disorders, administration	4 (2.2)	3 (1.6)
Hepatobiliary	1 (0.5)	0
Immune system	2 (1.1)	2 (1.1)
Infection/infestation[3]	**57 (31.0)[4]**	**22 (12.0)**
Injury, poisoning	8 (4.3)	8 (4.3)
Investigations	10 (5.4)	12 (6.5)
Metabolism/nutrition	5 (2.7)	2 (1.1)
Musculoskeletal	20 (10.9)	15 (8.2)
Neoplasms	1 (0.5)	1 (0.5)
Nervous system	13 (7.1)	10 (5.4)
Psychiatric	8 (4.3)	5 (2.7)
Renal/urinary	2 (1.1)	3 (1.6)
Reproductive/breast	5 (2.7)	4 (2.2)
Respiratory, thoracic, mediastinal	16 (8.7)	9 (4.9)
Skin, subcutaneous	6 (3.3)	7 (3.8)
Surgical and medical procedures	6 (3.3)	8 (4.3)
Vascular	6 (3.3)	5 (2.7)

[1]Subjects were counted once in each Body System.
[2]This table does not include the 127 subjects (41% of study population) who discontinued early.
[3]The first six month period included winter 2003/2004, so a seasonal increase in infections was expected compared to other seasons.
[4]Significant difference, $p < 0.05$.

There were no statistically significant increases in adverse event incidences during the second six months of the study, and overall, adverse events declined during the second six months of treatment for most body systems. The incidences of gastrointestinal disorders and infections/infestations were statistically higher during the first six months of the study; however, the winter season occurred during the first six months of the study and the natural seasonal increase in these disorders may be reflected here. Investigators enrolled subjects between July and November 2003. During the first six months there were more cases of upper respiratory infection, nasopharyngitis, and sinusitis.

Reviewer comment:

1. *A number of different factors may have theoretically contributed to the lower*

incidence of gastrointestinal disorders during the second six months of the study:

- *Decrease in viral gastrointestinal illnesses*
- *Decrease in GI effects of MiraLax with increased duration of use*
- *MiraLax dose reductions during the study (33 subjects had dose reductions).*

The 81 elderly subjects who completed Study 851-CR3 demonstrated a similar adverse event pattern during the first half and second half of the study. For most body systems (including GI), the adverse event incidences decreased during the second six months.

7.4.2.3 Explorations for drug-demographic interactions

The elderly subpopulation in Study 851-CR1 consisted of 75 individuals ages 65 years and older. The frequency of adverse events in this study was similar between MiraLax and placebo for elderly subjects. However, while there were no statistically significant differences in adverse event incidences between MiraLax and placebo treatment groups, the small sample sizes of this comparison should be noted. Compared to MiraLax-treated subjects, the placebo-treated elderly subjects had a numerically greater incidence of blood/lymphatic system adverse events and investigation-associated adverse events. Overall incidences of adverse events by MedDRA body system (including GI) were similar between the elderly subpopulation and the general study population for Studies 851-CR1 and 851-CR3. Elderly subjects treated with MiraLax did not experience greater incidences of adverse events by body system or GI adverse events specifically compared to the study population as a whole.

In Study 851-CR1, there were 29 males and 32 non-Caucasians treated with MiraLax. Analysis of the adverse event data by gender and race (Caucasian vs. non-Caucasian) showed no statistically significant drug-related differences in adverse event rates. Females had a higher incidence of infections (25.7%) than males (10.3%), mostly due to differences in the incidences of urinary tract infections and upper respiratory infections. Numerically, Caucasians experienced more diarrhea than non-Caucasians (18.6% vs. 9.4%) and more abdominal distension (5.2% vs. 0%).

Reviewer comment:

1. *As in most constipation studies, the majority of the population was Caucasian females. The male and non-Caucasian subpopulations are small and this may limit this study's ability to detect real differences between the adverse event profiles of males and females and among subjects of different racial and ethnic backgrounds.*

7.4.2.4 Explorations for drug-disease interactions

The sponsor conducted additional analyses on adverse event data and laboratory data to determine whether subjects with cardiac disease, renal disease, and/or diabetes experienced

a different or more severe adverse event profile than subjects without these higher risk medical conditions. Subjects with high risk conditions experienced a similar overall adverse event profile and similar incidences of GI adverse events. Higher incidences of metabolism and nutrition adverse event in the higher risk population were most likely related to the underlying medical conditions (especially hyperlipidemia) as suggested by the sponsor.

Table 41 compares the adverse event incidences of the higher risk and lower risk subpopulations by MedDRA Body System. Data are provided from studies 851-CR1 and 851-CR3. Study 851-ZCC was not included in this analysis due to the short study duration and the exclusion of all men and women over age 65 years.

Table 41: Comparison of adverse event (AE) rates in high risk subjects and low risk subjects from Protocols 851-CR1 and 851-CR3

Adverse Events	High Risk* (N = 99)	Low Risk (N = 416)
Patients with events	70 (70.7%)	285 (68.5%)
Number of events	241	560
MedDRA Body System	**N (%)**	**N (%)**
Blood/lymphatic	2 (2.0)	3 (0.7)
Cardiac disorders	3 (3.0)	4 (1.0)
Congenital, familial, genetic	0	1 (0.2)
Ear/labyrinth	3 (3.0)	8 (1.9)
Endocrine	0	4 (1.0)
Eye	2 (2.0)	5 (1.2)
Gastrointestinal	38 (38.4)	159 (38.2)
General disorders, administrations	6 (6.1)	21 (5.0)
Hepatobiliary	1 (1.0)	1 (0.2)
Immune system	1 (1.0)	4 (1.0)
Infection/infestation	29 (29.3)	100 (24.0)
Injury, poisoning, procedural	6 (6.1)	21 (5.0)
Investigations	10 (10.1)	32 (7.7)
Metabolism/nutrition	7 (7.1)	7 (1.7)
Musculoskeletal	18 (18.2)	45 (10.8)
Neoplasms	3 (3.0)	4 (1.0)
Nervous system	11 (11.1)	29 (7.0)
Pregnancy, puerperium, perinatal	0	1 (0.2)
Psychiatric	5 (5.1)	21 (5.0)
Renal/urinary	3 (3.0)	4 (1.0)
Reproductive/breast	2 (2.0)	12 (2.9)
Respiratory, thoracic, mediastinal	10 (10.1)	31 (7.5)
Skin, subcutaneous	3 (3.0)	18 (4.3)
Social circumstances	0	1 (0.2)
Surgical and medical procedures	3 (3.0)	13 (3.1)
Vascular	5 (5.1)	11 (2.6)

Table 42 summarizes and compares the incidences of GI adverse events experienced by the higher risk and lower risk study subpopulations.

Table 42: Comparison of GI adverse event incidence for *high risk* and *non-high risk* subjects treated with MiraLax (Protocols 851-CR1 and 851-CR3)

GI Preferred Term	High risk (N = 99) N (%)	Non-high risk (N = 416) N (%)
All GI disorders	38 (38.4)	159 (38.2)
Abdominal distension	1 (1.0)	17 (4.1)
Abdominal pain NOS	3 (3.0)	8 (1.9)
Diarrhea NOS	11 (11.1)	58 (13.9)
Flatulence	7 (7.1)	31 (7.5)
Loose stools	3 (3.0)	25 (6.0)
Nausea	6 (6.1)	23 (5.5)

7.4.2.5 Explorations for drug-drug interactions

Among 19 subjects using a drug with a narrow therapeutic index (NTI), there were no statistically significant differences in adverse event frequency. This subpopulation included subjects using the following drugs: warfarin, depakote, dilantin, digoxin, lithium, Synthroid, tegretol, and theophylline. Among 42 subjects using MiraLax and a NTI drug concomitantly, five had a change in NTI drug dose during the study. Three of these dose changes were clearly unrelated to MiraLax use. Investigators recorded the other dose change events as unrelated; however, this reviewer believes that the relationship between MiraLax use and the clinical events leading to dose change for phenytoin in one subject and for Synthroid in another subject are less certain.

The prescription labeling for MiraLax states that *no specific drug interactions have been demonstrated* between MiraLax and other drugs. MiraLax use does, however, affect bowel transport times. An article submitted by the sponsor as part of their literature review (Ragueneau et al 1999) suggests that co-administration of PEG 4000 (MiraLax is PEG 3350) and digoxin affects single-dose digoxin pharmacokinetics probably due to reduced intestinal absorption. There was a 40% reduction in mean C_{max} values and $AUC_{(0,t)}$ and $AUC_{(0,\infty)}$ mean values decreased by 30% compared to those following administration of digoxin alone.[19] It is possible that similar affects could occur with other narrow therapeutic index drugs.

Reviewer comment:

1. *Five of 42 subjects concomitantly using MiraLax and a NTI drug needed a change in drug dose at some time during the study. However, three of these events were*

[19] Ragueneau I, Poirier JM, Radembino N, Sao AB, Funck-Brentano, Jaillon P. Pharmacokinetic and pharmacodynamic drug interactions between digoxin and macrogol 4000, a laxative polymer, in healthy volunteers. Br J Clin Pharmacol. 1999; 48: 453 – 56.

clearly unrelated to MiraLax use, and the other two were unlikely related.

2. *Based on the article by Ragueneau et al (1999), digoxin pharmacokinetics are affected by coadministration of a PEG compound with a molecular weight about 20% greater than that of MiraLax. Patients using NTI drugs are usually monitored with serum levels on a regular basis. However, it may be valuable from a safety perspective to consider labeling language that instructs consumers who use NTI drugs to notify their healthcare provider of MiraLax use. While seven [redacted] days of use may not result in clinically significant changes in serum drug levels, repeated courses of treatment may. The label does not limit the number of times a consumer can repeat a one week course in one month's time. The label should include general language that instructs consumers to speak with a doctor before use if using other medicines.*

7.4.3 Causality Determination

Study 851-CR1 is the only study submitted in support of NDA 22-015 that was placebo-controlled. With the exception of GI adverse events, there were no significant differences in the incidences of adverse events between the placebo and MiraLax treated study populations.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Based on dose ranging information provided by the sponsor and data reviewed by this reviewer, the 17 g/day dose of MiraLax appears to be the dose that maximizes efficacy while minimizing adverse events in most adults.

MiraLax is currently labeled for a 14 day course of therapy, and the sponsor submitted draft OTC labeling that describes [redacted] course of therapy with the following warning and dosing instructions:

Stop use and ask a doctor if you need to use MiraLax for longer than [redacted]

Adults: [redacted] (17 g) or fill to top of white section in cap,

completely dissolve in 4 to 8 ounces beverage and drink – once daily.

Other laxatives currently marketed OTC are labeled for seven days of use. Efficacy data from study 851-6 submitted as a pivotal trial for the approval of prescription MiraLax demonstrated efficacy with seven days of therapy and study 851-3, the other pivotal study demonstrated efficacy with ten days of treatment. If the efficacy data from this application support efficacy of Miralax in relieving constipation in seven days, then the duration of use should be limited to seven days. This maximum duration of use should be clear in the Drug Facts label. The draft label already informs consumers to contact their physician if they do not have a bowel movement after four days of MiraLax therapy. The proposed MiraLax OTC label, consistent with currently marketed products, does not limit the frequency with which a consumer may repeat the course of treatment.

The sponsor needs to provide a method for consistently measuring or using a 17 g dose of Miralax.] [redacted] In addition, all clinical studies conducted have dissolved each 17 g dose of Miralax in 8 ounces of beverage. Based on clinical trial design and the fact that constipate individuals usually need to consume more fluid, the directions should instruct consumers to dissolve the 17 g of MiraLax in 8 ounces of beverage.

During all three clinical studies, investigators reduced the MiraLax dose in some subjects due to drug-related adverse events, most often gastrointestinal adverse events. Some of these dose reductions were temporary and some persisted until the end of study participation. Some subjects reduced their MiraLax dose in the first week of use. The draft OTC label fails to direct consumers on how to reduce dose and does not offer a lower dose option for individuals who experience loose stools or diarrhea. Instead, the label provides an instruction to *stop use and ask a doctor* if diarrhea, abdominal cramping, or bloating occur. This approach is an appropriate alternative to offering instructions for reducing dose; however, the current wording needs to be more specific and descriptive. This will be addressed in greater detail in the labeling review.

8.2 Drug-Drug Interactions

No specific drug-drug interactions have been identified with PEG 3350. However, as discussed earlier in this review, published literature suggests that co-administration of digoxin and PEG 3350 results in a significant reduction in C_{max} and AUC of digoxin. While this reviewer was unable to locate published information about decreased absorption of other drugs when taken with MiraLax, it is a theoretical possibility that should be addressed in labeling. OTC laxative monograph products carry similar labeling language.

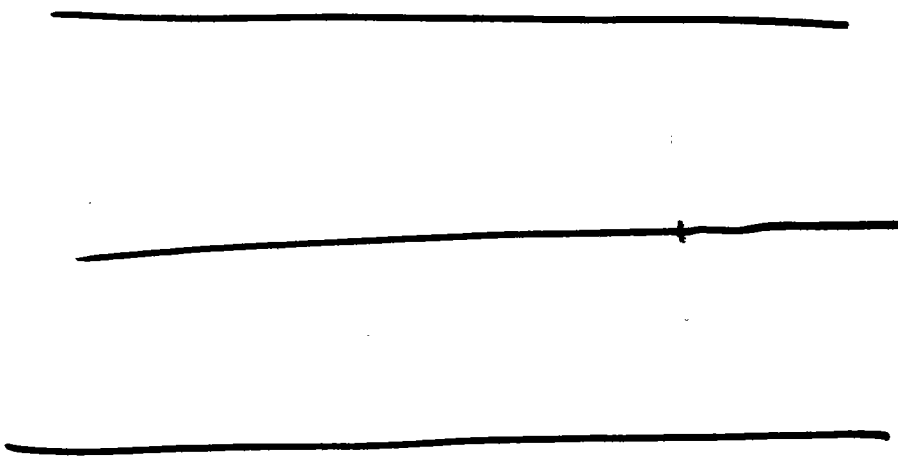
8.3 Special Populations

MiraLax 17 g/day was well tolerated in the elderly population of healthy, constipated adults even over six to 12 months of treatment. However, data from study 851-4, submitted to NDA 20-698, suggest that elderly, debilitated individuals in chronic care facilities may experience higher incidences of diarrhea.

There were no statistically significant differences in subjects' renal function from baseline to the ends of the studies, and there were no significant differences between subjects in the placebo and MiraLax treatment groups of study 851-CR1. However, individuals with compromised renal function may not tolerate laxative use as well as healthy individuals due to a reduced capacity to adjust to electrolyte and intravascular volume changes. It is appropriate to include a renal warning on the MiraLax OTC label consistent with that on the labels of other OTC laxative products.

8.4 Pediatrics

The sponsor submitted a request to defer studies in children ages two to sixteen years of age.



8.5 Advisory Committee Meeting

This application was not brought before an Advisory Committee.

8.6 Literature Review

See section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

The applicant did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

The applicant did not conduct actual use and label comprehension studies in support of this application as they were not requested by FDA.

9. OVERALL ASSESSMENT

9.1 Conclusions

MiraLax at a dose of 17 g/day has an appropriate safety profile for use as a nonprescription laxative in individuals ages 18 years and above.

Based on efficacy data from NDA 20-698 and NDA 22-015 (under current review), MiraLax provides effective treatment of constipation in seven days. Therefore, to optimize safe use in the OTC setting, the maximum labeled duration of use should be seven days. MiraLax should be approved for marketing only in single dose packages unless the sponsor provides an accurate dosing device that allows consumers to easily and reproducibly administer the correct dose of MiraLax. Each container should be limited to no more than two courses of therapy.

9.2 Recommendation on Regulatory Action

From a safety perspective, this application is approvable pending changes to the draft label and review of the Safety Update and postmarketing adverse event Medwatch forms, which have been requested but not received. If these materials are submitted, reviewed, and

found satisfactory prior to the PDUFA date, then this application should be approved.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The sponsor should submit required yearly and periodic reports.

9.3.2 Required Phase 4 Commitments

Pediatric studies in children ages two years and older should be deferred. Submission of a pediatric development plan may be deferred until further determination is made about provision of pediatric data under a written request for NDA 20-698.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

A copy of the proposed OTC label is located in the appendices under Other Pertinent Information, section 10.7 and a copy of the current prescription label is located in section 10.8. The review by Reynold Tan, Ph.D. provides a more thorough line-by-line labeling review. The following comments represent this reviewer's concerns and thoughts regarding the draft label and MiraLax OTC label content.

General comments:

- The prescription label for MiraLax contains the following contraindications, warnings, and precautions:
    - Use is contraindicated in patients with known or suspected bowel obstruction and those allergic to PEG

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-1

Additional comments:

-
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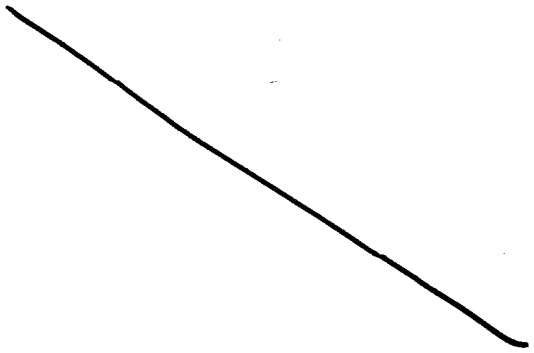

9.5 Comments to Applicant

At this time, it is not known whether the effect of PEG 3350 on colonic bacterial fermentation results in any clinically significant change in colonic epithelium over time. Based on the role that short chain fatty acids, such as butyrate, are believed to play in the colon, it may be informative, from a safety perspective, to follow consumers and patients who use PEG 3350 frequently for potential changes in colonic epithelium.

10. APPENDICES

10.1 Review of Individual Study Reports

This appendix contains the study design and methodology for the three Phase III clinical trials submitted to NDA 22-015: Study 851-CR1, Study 851-ZCC, and Study 851-CR3. The safety results from these studies were presented and discussed in Section 7 of this review. The efficacy results are presented in a separate review by Kristen Buck, MD, medical officer in DGP. This reviewer notes that the applicant did not provide a flow chart of study procedures for any of the three submitted clinical studies.

Braintree Study 851-CR1: Extended Use of MiraLax Laxative in Constipated Patients

This was a 50 center, randomized, double-blind, parallel-group, placebo-controlled, study designed to evaluate the safety and efficacy of extended (six month) use of MiraLax laxative compared to placebo in constipatied adult patients, including a subgroup of elderly

patients. The study enrolled normal, constipated outpatients and randomized them 2:1 to treatment with 17g per day of MiraLax or placebo (maltodextrin) for up to 180 days. The study used maltodextrin as the placebo, because prior studies demonstrated that maltodextrin does not affect constipation, and it resembles MiraLax in taste, appearance, density, and solubility,

To enroll, screened individuals met the following inclusion criteria:

- Constipated according to the modified ROME criteria-based study definition of constipation:
  - Less than three satisfactory stools per week
  - One or more of the following additional ROME-based criterion in more than 25% of defecations: straining, lumpy or hard stools, or sensation of incomplete evacuation
- On average, fewer than three satisfactory BMs per week during the 14 day observation period
- If female and of childbearing potential, patient must be surgically sterilized or using oral contraceptives, depot contraceptives, intrauterine device, or testifies that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so for the duration of the study
- Are otherwise in good health, as judged by a physical examination.

Screened individuals were excluded from the study for :

- Heme positive stool at screening
- Hypo- or Hyperthyroidism (by history or screening TSH)
- Suspected gastrointestinal perforation/obstruction
- History of gastric retention, inflammatory bowel disease (IBD), bowel resection, or colostomy
- Known organic cause for constipation
- Loose stools with sufficient criteria for irritable bowel syndrome (IBS):
  - In the last 12 months, 12 weeks of abdominal discomfort or pain with two of the following three features: relieved with defecation; onset associated with a change in frequency of stool; onset associated with a change in form of stool
- Using medication known to affect bowel habits
  - anti-diarrheals
  - antacids containing magnesium or aluminum salts
  - anticholinergics
  - antispasmodics
  - macrolides
  - octreotide
  - 5-HT_3 or 5-HT_4 receptor antagonists (e.g. Lotronex, Zofran, Zelnorm)
  - narcotics (except occasional codeine use for a non-GI condition allowed)
  - prokinetics
  - serotonin reuptake inhibitors or tricyclic antidepressants unless patient has been on a constant dose for at least one month prior to screening

  - calcium antagonists unless patient on a contant dose for at least one month prior to screening.
- Breastfeeding, pregnancy, or intent to become pregnant during the study
- Being a female patient of childbearing potential who refuses a pregnancy test
- Known allergy to corn or PEG
- Being a patient who, in the opinion of the investigator, should not be included in the study for any reason, including inability to follow study procedures
- Participating in an investigational clinical study in the past 30 days.

Eligible subjects were enrolled and randomized to one of the two treatment arms:
- MiraLax 17 g/day (N = 204)
- Placebo (N = 100)

Enrolled subjects had to stop all laxative use for a 14 day observation period during which they completed daily BM reports through an interactive voice response system (IVRS). The computer generated randomization schedule randomized subjects meeting constipation criteria by study site. The schedule used random-sized blocks of three balanced treatment assignments to insure the specified 2:1 treatment ratio. Subjects received their kit numbers sequentially according to the randomization schedule.

Subjects received their study drug and instructions to mix the contents of one packet (approximately 17 g) with eight ounces of juice or another beverage, and drink once daily. The study did not specify timing of the daily dose of study drug since MiraLax requires up to two days to induce a laxative effect in some patients. Subjects also received bisacodyl 5 mg tablets to use as a rescue medication. Instructions stated to use bisacodyl 10 mg if they experienced severe discomfort of no BM in four days. Study personnel told subjects to return to the study center at monthly intervals and to bring their remaining study drug and rescue medication to each visit.

Data collection occurred through two mechanisms: daily reports to the interactive voice response system (IVRS) and monthly study center visits. At monthly study center visits, study personnel reviewed any unused study drug and rescue medication and dispensed additional study drug and rescue medication as needed. In addition, subjects provided blood and urine samples for hematology, serum chemistry, and urinalysis. Subjects used the IVRS to provide daily reports on bowel habits and adverse events. Use of the system required patient identifiers and a security code. The IVRS prompted subjects to answer the following questions:
- How many stools did you pass today?
- How many satisfactory stools did you pass today?
- Did you have to strain to pass your stool today?
- Were your stools lumpy or hard today?
- Were your bowel movements complete?
- Did you take any laxatives, including rescue medicine today?
- Please rate the amount of cramping you experienced today on a scale of 0 – 4 with 0 indicating no cramping and 4 indicating extreme cramping.
- Please rate the amount of gas you had today on a scale of 0 – 4 with 0 indicating no

gas and 4 indicating extreme gas.
- Did you have 3 or more large watery stools today?

Every seventh day, the IVRS prompted the subject to answer the following global assessment question:

- In the past 7 days, do you feel you have had adequate relief of your constipation?

Safety assessments included adverse event monitoring and monthly hematology, serum chemistry, and urinalysis result monitoring. Vital signs were collected at screening physical examination and at monthly study site visits. The applicant presented adverse events descriptively by body system, preferred term, severity, and relationship to study treatment. Differences in adverse event rates between treatment groups were described using the Fishers Exact Test and further analyzed by factors for treatment group and visit using repeated measures ANOVA. The applicant tabulated the number and percent of patients who experienced a shift from baseline (low, normal, high) for each laboratory parameter.

The study's primary efficacy variable/endpoint was chosen based on discussion with FDA during drug development. The efficacy endpoints listed below are discussed in the efficacy review by Kristen Buck, MD:

- Primary efficacy variable/endpoint:
  Binary outcome based on overall treatment success (responder) or failure (non-responder). The definition of a treatment success or responder was:
  - Three or more satisfactory stools per week and
  - One or few of the following additional ROME-based criteria in more than 25% of defecations: straining, lumpy or hard stool, sensation of incomplete evacuation.
- Secondary efficacy endpoints:
  - ROME definition: a successful week defined as not satisfying any three of four ROME constipation symptom criteria without the aid of rescue medication or prohibited laxative. Only days with reported data counted toward the endpoint calculation
  - Super efficacy: a successful week was defined as not meeting any of the four ROME constipation criteria without the aid of rescue medication or prohibited laxative
  - Successful weeks by individual ROME constipation symptom. There was no requirement for a minimum number of treatment weeks for this endpoint.
  - Treatment weeks without use of rescue medication or prohibited laxative

There were two amendments to the protocol. Neither affected the conduct or outcomes of the study:

- Amendment 1 (instituted 06/17/2003):
  Clarified that IBS patients were excluded from study participation; stipulated immediate withdrawal of patients with hypo- or hyper-thyroidism based on baseline

TSH; allowed premature study discontinuation based on use of non-study laxatives or excluded medications

- Amendment 2 (instituted 09/29/2003):
  Clarified that patients with heme positive stools at baseline were eligible for study enrollment if the heme was attributable to hemorrhoids or anal fissures; clarified that subjects needed to discontinue use of fiber and herbal laxatives at screening; patients excluded if they had a colonoscopy within 30 days of screening visit; patients who previously used MiraLax were ineligble; patients that missed one day of IVRS reporting during the 14 day run-in were eligible for randomization as long as the missed reporting did not occur on Day 14.

Braintree Study 851-CR3: Open Label Study of Chronic MiraLax Use in Constipated Patients

This was a 50 center, open-label study designed to evaluate the safety of extended (one year) use of MiraLax laxative in constipated adult patients, including a subgroup of elderly patients. Subjects were normal, constipated adult outpatients who took 17g of MiraLax each day for up to 12 months. The investigators were allowed to decrease the subjects' daily dose in response to patient complaints of loose stools and/or discomfort.

To enroll, screened individuals met the following inclusion criteria:

- Constipated according to the modified ROME criteria-based study definition of constipation:
  - Less than three satisfactory stools per week
  - One or more of the following additional ROME-based criterion in more than 25% of defecations: straining, lumpy or hard stools, or sensation of incomplete evacuation
- If female and of childbearing potential, patient must be surgically sterilized or using oral contraceptives, depot contraceptives, intrauterine device, or testifies that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so for the duration of the study
- Are otherwise in good health, as judged by a physical examination
- In the investigator's judgment, the patient is mentally competent to sign an instrument of informed consent.

Screened individuals were excluded from the study for :

- Heme positive stool at screening
- Hypo- or Hyperthyroidism (by history or screening TSH)
- Suspected gastrointestinal perforation/obstruction
- History of gastric retention, inflammatory bowel disease (IBD), bowel resection, or colostomy
- Known organic cause for constipation

- Loose stools are present, and there is sufficient criteria for IBS:
  - In the last 12 months, 12 weeks of abdominal discomfort or pain with two of the following three features: relieved with defecation; onset associated with a change in frequency of stool; onset associated with a change in form of stool
- Using medication known to affect bowel habits
  - anti-diarrheals
  - antacids containing magnesium or aluminum salts
  - anticholinergics
  - antispasmodics
  - macrolides
  - octreotide
  - 5-HT_3 or 5-HT_4 receptor antagonists (e.g. Lotronex, Zofran, Zelnorm)
  - narcotics (except occasional codeine use for a non-GI condition allowed)
  - prokinetics
  - serotonin reuptake inhibitors or tricyclic antidepressants unless patient has been on a constant dose for at least one month prior to screening
  - calcium antagonists unless patient on a constant dose for at least one month prior to screening.
- Breastfeeding, pregnancy, or intent to become pregnant during the study
- Being a female patient of childbearing potential who refuses a pregnancy test
- Known allergy to PEG
- Being a patient who, in the opinion of the investigator, should not be included in the study for any reason, including inability to follow study procedures
- Participating in an investigational clinical study in the past 30 days.

Subjects received a 527 g bottle of MiraLax. Instructions told subjects to mix one capful of MiraLax (approximately 17 g) in eight ounces of juice or other beverage, and drink once daily for up to 12 months. Subjects received bisacodyl 5 mg tablets and could use bisacodyl 10 mg to treat severe discomfort due to constipation or lack of BM for four days. The protocol did not specify timing of the MiraLax dose. Subjects were instructed to return to the study center for follow-up visits at 2, 4, 6, 9, and 12 months following enrollment and to bring remaining study drug and rescue medication with them. Study personnel completed the following activities during these visits:

- Reviewed unused medications for accountability and treatment compliance
- Dispensed additional study drug and rescue medication as needed
- Collected blood and urine samples
- Reviewed adverse events
- Asked the following global efficacy question: *Consider how you felt since your last visit in regard to your constipation, in particular, your overall well being, number of BMs, consistency and completeness of your BMs, and symptoms of straining. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms since your last visit (completely relieved, considerably relieved, somewhat relieved, unchanged, or worse)?*

  A follow-up question requested information on the specific ROME constipation criteria: *Since your last visit, have you experienced the following: less than 3*

satisfactory BMs per week; straining in more than 25% of your BMs, lumpy or hard stool more than 25% of the time; sensation of incomplete evacuation following more than 25% of your BMs?

During the course of the study, investigators could decrease a subject's MiraLax dose based on complaints of loose stools and/or discomfort but could not increase the MiraLax dose beyond 17 g per day for any reason.

The applicant presented results by pooling global efficacy assessments, ROME symptoms, adverse events, and laboratory results across all study sites and descriptively summarizing these results by visit. Results of laboratory tests were summarized based on mean actual change from baseline for continuous assessments. Global efficacy responders were those who reported complete or considerable relief. A constipation responder was someone who had three or more satisfactory BMs per week and did not have more than one of the three remaining ROME criteria. Missing subject data for a specified visit was classified as *missing* and not as a *non-responder* for that visit.

The applicant reported treatment emergent adverse events by body system, preferred term, severity, and relationship to study drug. The primary safety comparison was for adverse events and laboratory values during the first six months of the study compared to those during the second six months of the study. The study report describes laboratory results as mean change from baseline for each visit and the number (%) subjects who experienced a shift in normal range (low, normal, high) between baseline and any assessment period during the study.

Plasma PEG 3350 levels were determined in a subset of subjects by a validated HPLC/MS/MS assay. The applicant reported these findings in a separate pharmacokinetic study report (851-CR3-PK).

There were two amendments to the protocol. Neither affected the conduct or outcomes of the study:

- Amendment 1 (instituted 06/17/2003):
  Clarified that IBS patients were excluded from study participation; stipulated immediate withdrawal of patients with hypo- or hyper-thyroidism based on baseline TSH; allowed premature study discontinuation based on use of non-study laxatives or excluded medications.

- Amendment 2 (instituted 09/29/2003):'
  Clarified that patients with heme positive stools at baseline were eligible for study enrollment if the heme was attributable to hemorrhoids or anal fissures; clarified that subjects needed to discontinue use of fiber and herbal laxatives at screening.

Braintree Study 851-ZCC: MiraLax vs. ZELNORM in the Treatment of Patients With Chronic Constipation

This was a 25 center, randomized, open-label, parallel arm, multi-center study designed to evaluate the safety and efficacy of MiraLax laxative compared to Zelnorm in adult patients with constipation. The study enrolled normal constipated patients who were randomized to treatment with either 17g of MiraLax per day or 6 mg Zelnorm twice daily (BID) for 28 days.

To enroll, screened individuals met the following inclusion criteria:

- Constipated according to the modified ROME criteria-based study definition of constipation:
  - Less than three satisfactory stools per week
  - One or more of the following additional ROME-based criterion in more than 25% of defecations: straining, lumpy or hard stools, or sensation of incomplete evacuation
- If female and of childbearing potential, patient must be surgically sterilized or using oral contraceptives, depot contraceptives, intrauterine device, or testifies that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so for the duration of the study
- Are otherwise in good health, as judged by a physical examination.
- In the investigator's judgment, patient is mentally competent to sign an instrument of informed consent

Screened individuals were excluded from the study for :

- Heme positive stool at screening not associated with hemorrhoids or anal fissures
- Hypo- or Hyperthyroidism (by medical history)
- Severe renal impairment
- Moderate or severe hepatic impairment
- Known or suspected gastrointestinal perforation/obstruction
- History of gastric retention, inflammatory bowel disease (IBD), bowel resection, or colostomy
- Symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions
- Known organic cause for constipation
- Using medication known to affect bowel habits
  - anti-diarrheals
  - antacids containing magnesium or aluminum salts
  - anticholinergics
  - antispasmodics
  - macrolides
  - octreotide
  - 5-HT_3 or 5-HT_4 receptor antagonists (e.g. Lotronex, Zofran, Zelnorm)
  - narcotics (except occasional codeine use for a non-GI condition allowed)
  - prokinetics
  - serotonin reuptake inhibitors or tricyclic antidepressants unless patient has been

on a constant dose for at least one month prior to screening
- calcium antagonists unless patient on a contant dose for at least one month prior to screening.

- Breastfeeding, pregnancy, or intent to become pregnant during the study
- Being a female patient of childbearing potential who refuses a pregnancy test
- Known allergy to Zelnorm (or any of its exciptients) or PEG
- Being a patient who, in the opinion of the investigator, should not be included in the study for any reason, including inability to follow study procedures
- Participating in an investigational clinical study in the past 30 days
- Undergoing colonoscopy within 30 days of screening
- Currently using or previously using MiraLax or Zelnorm.

A SAS program randomization schedule randomized subjects within each participating study site 1:1 to the following treatment groups:

- MiraLax 17 g/day dissolved in 8 oz. juice or other beverage
- Zelnorm 6 mg BID before meals (maximum recommended dose of Zelnorm for treatment of chronic constipation).

The protocol allowed subjects to use bisacodyl 5 mg tablets in a 10 mg dose to treat severe discomfort or lack of BM in four days while using assigned study medication. Following randomization, study personnel dispensed study drug and rescue medication to the study subjects and instructed them to return to the study center for a follow-up visit following 28 days of treatment. Subjects used the IVRS to report their daily BM experiences. The IVRS questionnaire used was the same as that outlined in Study 851-CR1 above.

Adverse events monitoring occurred through evaluation of IVRS responses. The applicant presented treatment emergent adverse event rates by body system, preferred term, severity, and relationship to treatment for each treatment group. Differences in adverse event rates between treatment groups were assessed using Fishers Exact Test.

Primary and secondary efficacy endpoints for this study were identical to those in Study 851-CR1 described above.

The 851-ZCC study plan was affected by three protocol amendments. Amendment 1 was implemented prior to enrollment; however, Amendments 2 and 3 were implemented after enrollment began.

- Amendment 1 (instituted 04/27/2004 – prior to enrollment):
  Disallowed dose increases in study medication; added reporting time frames for adverse events and serious adverse events; added guidelines for handling patients experiencing diarrhea; added an accepted visit window for study visit 2; added supporting information for planned statistical analyses; clarified that there were no blood draws for laboratory analysis.

- Amendment 2 (instituted 06/10/2004:
  Clarified that patients with a prior diagnosis of IBS would be excluded from the

study

- Amendment 3 (instituted 07/23/2004):
  Modified study inclusion criteria to exclude all patients who were elderly or male. Elderly and male subject enrolled prior to amendment approval were allowed to complete the study. This amendment was triggered by the 07/14/2004 FDA Advisory Committee recommendation that approval of Zelnorm for chronic constipation be limited to females under the age of 65 years.

10.2 Line-by-Line Labeling Review

Please see the review in DFS by Reynold Tan, Ph.D.

Other Pertinent Information: Additional Tables

10.3 Severe Adverse Events

Table 10.3: Serious Adverse Events Among Subjects From Clinical Studies

Subject	Age (yr) Gender	Treatment Start Date	Event Date/Description	Outcome	Related to study drug?
Study 851-PK-004/006					
003	38 M	-	Following discharge from the study the subject went on a cocaine binge and missed his scheduled renal dialysis. He developed chest pain and shortness of breath (SOB) that progressed to worsening chest pain accompanied by volume overload. He was hospitalized and dialyzed.	Discharged from hospital.	Unrelated
Study 851-CR1 (MiraLax)					
122-010	67 M	03/17/2004	06/18/2004: Diagnosed with prostate cancer. Surgery scheduled	06/24/2004: discontinued	Unrelated
131-006	55 F	04/23/2004	[redacted] Presented to ER complaining of substernal chest pain for one hour, SOB, bilateral arm numbness, and nausea. Pain spontaneously resolved. Hospitalized and MI ruled out. Exercise stress test revealed no acute ST changes at peak exercise. Treated for chest pain, dehydration, and low potassium.	[redacted] Discharged home. MiraLax treatment interrupted for 2 days.	Unrelated
132-003	64 F	01/06/2004	[redacted] Presented to ER with a two week history of dyspnea on exertion and weakness. On exam, she had SOB and 1+ ankle edema. Admitted to hospital. Adenosine thallium stress test revealed normal left ventricular function and no reversible perfusion abnormalities. Doppler studies showed mild tricuspid regurgitation, mild to moderate mitral regurgitation, and trace pulmonic insufficiency.	[redacted] Discharged home.	Unrelated
149-019	59 F	05/05/2004	[redacted] : Taken to ER with seizure, loss of consciousness, and head trauma due to a fall. Medical history significant for seizure disorder (Jacksonian, generalized tonic/clonic). Admitted to hospital with the following diagnoses: seizure disorder, hypertension, depression, scalp laceration, and concussion.	Treated and discharged. Stopped MiraLax for one day.	Unrelated
Study 851-CR1 (Placebo)					

Table 10.3: Serious Adverse Events Among Subjects From Clinical Studies

Subject	Age (yr) Gender	Treatment Start Date	Event Date/Description	Outcome	Related to study drug?
108-012	47 F	04/28/2004	Discontinued MiraLax on 08/23/2004. Routine mammogram revealed left breast calcifications. Biopsy was positive for breast cancer. .	Subject underwent double mastectomy on [redacted]	Unrelated
113-004	75 F	05/06/2004	06/16/2004: Discontinued MiraLax 07/13/20004: Subject underwent upper GI series and colonoscopy as part of a workup for anemia. Diagnosed with gastric cancer on upper GI and this was later confirmed by biopsy that revealed poorly differentiated adenocarcinoma of the antrum.	Subject underwent distal partial gastrectomy on [redacted]. The tumor was confined to the lamina propria without apparent local invasion but one regional lymph node showed metastatic disease. Treated with chemotherapy and radiation.	Unrelated
117-006	52 F	12/18/2003	03/07/2004: Study drug discontinued. 04/14/2004: Positive stool hemocult noted on rectal exam. 04/15/2004: Colonoscopy revealed a tubulovillous adenoma in the rectosigmoid colon. 04/22/2004: Abdominal CT revealed a mass in the posterior segment of the right hepatic lobe suspicious for metastasis. 05/05/2004: Barium enema shows a lesion suspicious for circumferential adenocarcinoma of the sigmoid colon.	[redacted] Exploratory laparatomy with excision of primary tumor and liver metastasis. Intrahepatic pump placed. 07/13/2004: Chemotherapy started.	Unrelated
119-014	24 F	04/17/2004	[redacted]: Presented to the ER with progressive right sided pain, nausea, and vomiting. Abdominal CT scan showed a right hydronephrosis and proximal hydroureter with a 4 mm ureteral stone. Urinalysis negative for infection. Admitted to hospital and underwent cystoscopy with retrograde right ureteroscopic stone extraction followed by laser lithotripsy and right uretera stent placement.	[redacted] Discharged home.	Unrelated
134-012	51 F	05/26/2004	[redacted]: Subject reported a panic attack that required overnight hospitalization.	[redacted] Discharged home. MiraLax interrupted for two days.	
Study 851-CR3					

Table 10.3: Serious Adverse Events Among Subjects From Clinical Studies

Subject	Age (yr) Gender	Treatment Start Date	Event Date/Description	Outcome	Related to study drug?
101-050	49 F	08/23/2003	[redacted] Subject saw primary care provider (PCP) for lightheadedness, nausea, and numbness and was referred to the ER. CT scan of the head revealed a possible lacunar infarct in the right basal ganglia. Admitted to hospital and underwent head MRI and lumbar puncture which were normal. Discharge diagnosis: disequilibrium of unclear etiology.	[redacted] Discharged home.	Unrelated
102-002	75 F	09/23/2003	[redacted]: Surgical repair of right rotator cuff tear.	[redacted] Discharged home. Missed one day of MiraLax.	Unrelated
107-057	58 F	07/16/2003	[redacted]: Admitted to the hospital and treated for an exacerbation of asthmatic bronchitis. Portable chest film was consistent with prior films	[redacted] Discharged home.	Unrelated
111-014	57 F	08/08/2003	[redacted]: Presented to ER with severe lower back pain and was admitted to the hospital. CT and plain films showed arthritic changes and a bulging disc in the lower back. Treated for lower back pain.	[redacted] Discharged Home. Missed two days of MiraLax	Unrelated
113-142	43 F	10/07/2003	[redacted] Due to a history of traumatic brain injury, subject lost her balance and fell at home. She landed on her right knee and struck her left shoulder and hand. Presented to ER and was diagnosed with a fractured left 5th finger and a contusion of the right knee. She was admitted to the hospital for observation. An unsuccessful attempt was made to aspirate a hematoma from the right knee bursa.	[redacted] Discharged home.	Unrelated
114-214	84 M	08/12/2003	[redacted] Admitted to hospital for sudden onset of weakness and numbness on the left side. Head CT showed old encephalomalacia of the left frontal cortex and left posterior frontal white matter but no acute ischemic or hemorrhagic lesion. Head MRI showed an acute right front parietal infarct. Carotid duplex dopplers showed Class D disease on the left and Class C on the right.	[redacted] Discharged to a rehabilitation hospital.	Unrelated

Table 10.3: Serious Adverse Events Among Subjects From Clinical Studies

Subject	Age (yr) Gender	Treatment Start Date	Event Date/Description	Outcome	Related to study drug?
114-215	32 F	09/22/2003	[redacted] Hospitalized for acute pyelonephritis. Developed secondary septic shock, acute respiratory failure, metabolic acidosis, and nosocomial pneumonia. Treated with antibiotics. Placed on life support. Recovered.	[redacted] Discharged home.	Unrelated
115-289	81 M	08/22/2003	07/14/2004: Subject had a routine ECG that was abnormal. 07/21/2003: A repeat ECG with his PCP was also abnormal. A cardiologist performed a stress test and echocardiogram which were abnormal. Subject was admitted to the hospital for angioplasty and stent placement for a 90% coronary arterial blockage.	Not provided.	Unrelated
122-025	46 M	07/24/2003	[redacted]. Esophageal web dilated during endoscopy. Esophageal biopsy performed. Subject had one prior esophageal dilation. Discharged following the procedure and developed abdominal pain on the way home. Presented to the ER and barium swallow revealed esophageal perforation above the esophago-gastric junction. Subject underwent laparotomy with perforation repair on [redacted] Esophageal biopsy revealed adenocarcinoma-in-situ. Subject discharged home and later readmitted on [redacted] for esophagogastrectomy.	Not provided.	Unrelated
129-424	68 F	10/23/2004	11/26/2003: Subject had a history of osteoarthritis of the back and noted worsening back pain. Back pain continued to worsen. On [redacted], subject had a spinal fusion at L4-L5 for degenerative spondylolisthesis and stenosis.	[redacted] Discharged home. Stopped MiraLax from 05/30 – 06/08/2004.	Unrelated
130-173	71 F	10/01/2003	[redacted] Presented to ER with a dislocated hip. On [redacted], patient was taken to the operating room to attempt a closed reduction, which was unsuccessful. On [redacted] the patient underwent extraction of the femoral head and implantation of a cement-less femoral stem.	[redacted] Discharged to an extended care facility.	Unrelated

Table 10.3: Serious Adverse Events Among Subjects From Clinical Studies

Subject	Age (yr) Gender	Treatment Start Date	Event Date/Description	Outcome	Related to study drug?
132-083	34 F	10/20/2003	[redacted] Subject had sickle cell disease and presented to the hospital with a complaint of sickle crisis. She had SOB, arthropathy, and arthralgias. In the hospital she received hydration and potassium supplementation. The crisis resolved in 48 hours.	[redacted] Discharged home. MiraLax stopped during hospitalization.	Unrelated
134-145	60 F	08/21/2003	[redacted] Admitted to hospital for surgical decompression and repair of torn rotator cuff of right shoulder.	[redacted] Discharged home.	Unrelated
135-417	49 F	10/30/2003	12/23/2003: Developed symptoms of sinus infection. [redacted] Presented to ER with headache, nasal congestion, and earache. Admitted to hospital with diagnosis of pansinusitis and acute otitis media.	[redacted] Discharged home. MiraLax interrupted while hospitalized.	Unrelated
142-270	69 F	10/06/2003	08/21/2003: Weak, diaphoretic, repeatedly passing out [redacted]. Presents to ER. Blood pressure = 85/60, pulse = 130, hemocult positive. Admitted to hospital for weakness and occult gastrointestinal bleeding.	[redacted] Discharged home. Condition improved and Hemoglobin = 8.1.	Unrelated
146-043	29 F	07/21/2003	[redacted] Reported pregnancy to study staff. Underwent dilation and curettage on [redacted] for pregnancy termination at 7 weeks gestation.	No complications. MiraLax discontinued 10/06/2003.	Unrelated
147-089	69 M	10/23/2003	[redacted] Admitted to hospital and underwent right total knee arthroplasty for a history of severe degenerative joint disease.	[redacted] Discharged home.	Unrelated
149-402	86 M	09/23/2003	Discontinued MiraLax use on 02/01/2004. On [redacted] the subject fell at home and fractured his left scapula and hip. He was hospitalized and was treated with bedrest, mobilization, and physical therapy.	[redacted] Transferred to a rehabilitation/assisted living facility.	Unrelated

10.4 Line Listing of subjects with MiraLax dose reduction

Table 10.4: Adverse event initiated MiraLax dose reductions in subjects from Studies 851-CR1 and 851-CR3

Subject	Demographics	Dose	Study Days	Adverse Event	Severity	Outcome
Study 851-CR1						
101-5	F, 69 yo, Cauc.	8.5 g QD	6 – 28	Rectal irritation Watery stools	Mild	Resolved
102-17	M, 29 yo, AA	17 g QOD	15 – 45	Intermittent watery stool	Mild	Resolved
119-11	M, 78 yo Cauc.	4.3 g QD	10 – 11, 39	Diarrhea	Moderate	Resolved
119-13	F, 36 yo Cauc.	ND*	3	Diarrhea	Moderate	Unresolved D/C
120-5	F, 63 yo, Cauc.	ND	36 – 48	Increased BM frequency	Mild	Resolved
124-1	F, 49 yo, Asian	ND	1 – 16	Nausea	Moderate	Resolved. At visit 8 was using 17 g/day.
124-2	F, 69 yo, Cauc.		4 – 6	Diarrhea	Severe	D/C study Day 26
129-13	F, 63 yo, AA	8.5 g QOD	6 – 12 6 - 29	Diarrhea Fecal urgency	Moderate	Resolved
130-11			85 – 87	Defecation urgency Diarrhea	Moderate	Resolved
132-1	M, 75 yo, Cauc.	8.5 g	56 – 63	Loose stools	Mild	Resolved. Later D/C study for flatulence
135-1	F, 58 yo Cauc.	8.5 g QD	3 – 34	Watery stools Diarrhea	Mild	Resolved
135-7	F, 47 yo Cauc.	ND	111 – 114	Gastroenteritis, viral	Severe	Resolved. Reduced two doses during GI virus
135-20	F, 53 yo Cauc.	8.5 g QD	6 – 8	Watery stools	Moderate	Resolved
135-21	F, 49 yo Cauc.	8.5 g QD	11 – 14	Watery stools	Moderate	Resolved
141-14	F, 67 yo, Cauc.	8.5 g	35	Diarrhea	Moderate	Resolved
143-2	F, 56 yo Cauc.	8.5 g QD	16	Loose stool	Moderate	Unresolved
143-10	F, 5 yo Cauc.	8.5 g QD	5	Watery stools Abd* cramping	Severe	Resolved. Increased dose to 17 g QD before end of study
149-23	F, 32 yo Cauc.	8.5 g QD	0 – 30	Bloated	Mild	Resolved
Study 851-ZCC						
117-8	F, 22 yo Cauc.	ND	3 - 6	Diarrhea	Mild	Resolved

Table 10.4: Adverse event initiated MiraLax dose reductions in subjects from Studies 851-CR1 and 851-CR3

Subject	Demographics	Dose	Study Days	Adverse Event	Severity	Outcome
129-2	F, 64 yo AA	ND	11 - 24	Gas	Moderate	Resolved
129-4	F, 46 yo Cauc.	ND	ND	Abdominal cramping Left hand and foot swelling GERD worsening Dehydration	Mild	Dehydration resolved. Others unresolved. Used only 7 packets of MiraLax.
135-6	F, 34 yo Cauc.	8.5 g QD	13-18	Watery stool	Moderate	Resolved
Study 851-CR3						
101-52	F, 63 yo, Cauc.			Abdominal bloating	Mild	
103-101	F, 71 yo, Cauc.		33 – 39	Diarrhea	Moderate	Resolved
107-55	F, 33 yo, Cauc.		9 – 64	Diarrhea	Mild	Resolved
107-59	F, 72 yo, Cauc.		124 – 151	Diarrhea		Resolved
110-66	F, 68 yo, Cauc.		3 – 72	Increased flatulence	Severe	Resolved but mild recurrence Days 133 - 257
111-17	M, 42 yo, AA		15	Flatulence	Moderate	Unresolved
116-24	F, 42 yo, AA		31 – 38	Diarrhea	Mild	Resolved
118-153	F, 60yo, Am Ind					
118-154	F, 62 yo, Cauc.		28 – 48	Loose stools with stool leakage	Moderate	Resolved
119-262	F, 64 yo, Cauc.		112 – 119	Loose stools	Moderate	Resolved
129-69	M, 86 yo, Cauc		?	Excessive stool frequency		Resolved
129-71	F, 73 yo, Cauc.		8 – 30	Abd cramping, excessive stool frequency, flatulence	Mild	Resolved
129-72	F, 52 yo, Cauc.		5 – 42	Flatulence Fecal incontinence	Moderate	Resolved except mild flatulence D 43 - 74
129-422	F, 52 yo, Cauc.		243	Excessive gas	Mild	Resolved
129-423	F, 66 yo, AA		121 – 274	Flatulence	Mild	Resolved
132-79	F, 50 yo, Cauc.		133 – 140	Abd cramping Loose stools	Mild	Resolved
132-80	F, 47 yo, Cauc.		15	Abd cramping Gas pains	Moderate	Resolved
132-81	F, 77 yo, AA		2 – 9	Diarrhea	Moderate	Resolved
132-84	M, 75 yo, Cauc.		13 – 22	Diarrhea	Moderate	Resolved and then mild recurrence D 140 – 147
134-146	F, 41 yo, Cauc.		1 – 5	Diarrhea	Moderate	Resolved

Table 10.4: Adverse event initiated MiraLax dose reductions in subjects from Studies 851-CR1 and 851-CR3

Subject	Demographics	Dose	Study Days	Adverse Event	Severity	Outcome
135-198	F, 68 yo Cauc.		4 – 109	Flatulence Nausea, Day 5 Indigestion, Day 2-3	Mild Mild Moderate	Discontinued study for indigestion Days 90 - 109
135-416	F, 65 yo, Cauc.		259 243 – 276	Pulmonary Edema Watery stool	Moderate	Pulmonary edema not resolved Watery stool resolved
136-232	F, 79 yo, Cauc.		4 – 5	Diarrhea	Moderate	Resolved
139-190	F, 40 yo, Cauc.		10 – 12	Loose stools	Mild	Resolved
139-192	F, 58 yo, Cauc.		40	Abd bloating	Mild	Discontinued study for fecal incontinence, Day 101
140-205	F, 45 yo, Cauc.		5 – 9 351 - 377	Diarrhea Diarrhea (2^{nd} ↓)	Mild	Resolved but recurrence
142-268	M, 91 yo, Cauc.		199	Blood in sputum	Mild	Resolved
143-202	F, 46 yo, Cauc.		13 – 22	Nausea	Moderate	Resolved
143-204	F, 70 yo, Cauc.		39 – 353	Loose stools	Moderate	Resolved
146-308	F, 75 yo, Cauc.		17 – 43 17 – 42	Increased flatulence Loose stools	Mild	Resolved
148-6	M, 94 yo, Cauc.		11 – 13	Diarrhea	Mild	Resolved
148-182	M, 70 yo, Cauc.		8 – 57	Diarrhea	Mild	Resolved
149-282	F, 38 yo, Cauc.		8 – 57	Loose stools	Mild	Resolved

* ND = not documented on CRF

10.5 Tables of Laboratory Results Presented by Study

The following pages contain tables of chemistry, hematology, and urinalysis results. The results are presented by laboratory visit, by test, and by study. The tables include normal ranges, mean values, and ranges of subject values.

Table 10.5a: Chemistries - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3								
Laboratory Assessment (normal range)	**Normal Range**	**Lab Visit***	**851-CR1 Placebo**		**851-CR1 MiraLax**		**851-CR3 MiraLax**	
			Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
Albumin (g/dL)	3.4 – 4.5	Base	4.08	3.3 – 4.6	4.10	3.4 – 5.0	4.10	3.2 – 5.0
		2	4.02	3.3 – 4.6	4.00	3.2 – 4.7	3.99	3.1 – 5.3
		3	3.98	3.5 – 4.5	4.03	3.2 – 4.9	3.97	3.3 – 4.7
		4	4.07	3.5 – 4.8	4.05	3.3 – 4.8	3.99	3.4 – 4.8
		5	3.98	2.9 – 4.5	4.03	3.1 – 4.8	4.03	3.2 – 5.2
		6	3.96	3.6 – 4.5	4.01	3.3 – 4.6	4.00	3.0 – 4.7
Alkaline Phosphatase (IU/L)	26 - 99	Base	70.6	28 – 136	65.0	19 – 135	67.5	25 – 154
		2	65.3	30 – 138	65.1	23 – 142	68.8	30 – 142
		3	66.4	39 – 176	63.1	19 – 125	70.8	28 – 210
		4	68.1	30 – 196	62.4	23 – 130	67.7	30 – 149
		5	71.5	31 – 264	61.5	21 – 148	67.2	28 – 141
		6	67.2	29 – 224	60.2	14 – 151	66.8	21 - 133
ALT (IU/L)	10 - 28	Base	22.1	8 – 104	20.6	8 – 103	20.5	8 – 119
		2	20.9	9 – 68	19.8	8 – 51	20.7	7 – 113
		3	21.5	10 – 72	19.8	9 – 48	20.2	0 – 86
		4	21.9	10 – 64	19.6	8 – 52	20.8	8 – 71
		5	23.5	9 – 110	20.4	7 – 83	22.0	7 – 207
		6	21.0	8 – 68	20.7	8 – 137	19.9	9 - 69
Amylase (IU/L)	36 - 128	Base	80.7	15 – 265	79.1	17 – 394	82.2	15 – 232
		2	79.3	22 – 273	79.0	16 – 303	79.8	24 – 201
		3	77.7	29 – 191	79.1	20 – 337	81.0	23 – 209
		4	79.6	29 – 196	79.0	18 – 346	79.8	21 – 345
		5	74.7	35 – 146	78.1	15 – 195	78.2	19 – 194
		6	80.0	32 – 209	79.1	19 – 235	77.1	24 - 204
AST (IU/L)	13 - 35	Base	24.8	14 – 74	23.3	13 – 62	24.3	14 – 99
		2	24.7	15 – 65	23.7	13 – 42	24.0	11 – 75
		3	25.3	14 – 53	23.0	13 – 42	24.0	13 – 56
		4	25.4	13 – 63	22.9	10 – 45	24.7	14 – 79

Table 10.5a: Chemistries - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3

Laboratory Assessment (normal range)	Normal Range	Lab Visit*	851-CR1 Placebo		851-CR1 MiraLax		851-CR3 MiraLax	
			Mean	Range	Mean	Range	Mean	Range
		5	25.6	14 – 80	23.9	13 – 77	26.7	14 – 152
		6	23.5	15 – 43	23.9	12 – 71	24.4	12 - 71
Bicarbonate (mEq/dL)	23 – 29	Base	25.5	21 – 31	25.2	18 – 32	25.2	18 – 32
		2	25.5	20 – 31	25.2	19 – 30	25.3	17 – 42
		3	25.4	18 – 32	25.3	18 – 33	25.7	19 – 34
		4	25.2	20 – 36	25.2	18 – 30	25.4	19 – 35
		5	25.2	21 – 33	25.2	18 – 32	24.6	16 – 30
		6	25.9	21 – 32	25.1	19 – 30	25.1	18 - 31
BUN (mg/dL)	6 - 20	Base	12.8	5 – 39	13.0	5 – 31	13.3	6 – 43
		2	13.1	6 – 35	13.4	5 – 34	13.7	5 – 52
		3	12.5	5 – 29	13.0	5 – 34	13.4	5 – 42
		4	12.3	6 – 24	13.8	6.– 39	13.6	6 – 39
		5	13.6	6 – 25	13.0	5 – 30	14.4	6 – 43
		6	13.2	8 – 22	13.2	5 – 40	13.9	5 - 40
Calcium (mg/dL)	8.6 – 10.0	Base	9.58	8.6 – 10.7	9.53	8.5 – 10.9	9.6	8.5 – 11.5
		2	9.46	8.6 – 10.3	9.45	8.4 – 10.7	9.5	6.6 – 11.3
		3	9.52	8.7 – 10.5	9.50	8.5 – 10.7	9.5	8.3 – 9.4
		4	9.55	9.0 – 10.7	9.50	8.5 – 10.7	9.5	7.6 – 10.7
		5	9.47	8.5 – 10.2	9.52	8.4 – 10.7	9.5	7.4 – 11.0
		6	9.50	8.9 – 10.2	9.49	8.5 – 10.6	9.5	8.4 – 10.7
Chloride (mEq/dL)	98 - 107	Base	104.2	96 - 109	104.6	93 – 115	104.0	92 – 111
		2	104.3	96 - 114	104.8	90 - 112	104.7	95 – 114
		3	105.0	100 - 113	104.4	96 - 113	104.4	94 – 116
		4	104.3	98 - 112	104.3	93 - 112	104.8	95 – 115
		5	104.2	94 - 110	104.5	97 - 112	104.4	94 – 110
		6	104.0	94 - 109	104.4	95 - 112	104.0	94 - 114
Creatine Kinase (IU/L)	49 - 234	Base	118	21 - 648	112	24 - 1770	112	21 - 1042
		2	114	17 - 994	106	22 - 430	107	26 – 658
		3	95	27 - 256	110	22 - 477	113	23 – 1694
		4	117	33 - 573	105	22 - 334	102	23 - 764

Table 10.5a: Chemistries - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3

Laboratory Assessment (normal range)	Normal Range	Lab Visit*	851-CR1 Placebo		851-CR1 MiraLax		851-CR3 MiraLax	
			Mean	Range	Mean	Range	Mean	Range
		5	97	30 - 390	102	26 - 383	104	23 – 768
		6	100	29 - 349	109	22 - 375	107	23 - 1038
Creatinine (mg/dL)	0.6 – 1.1	Base	0.9	0.5 – 1.9	0.8	0.5 – 1.8	0.9	0.4 – 2.9
		2	0.9	0.5 – 2.3	0.9	0.5 – 1.8	0.9	0.5 – 3.0
		3	0.8	0.5 – 1.3	0.9	0.6 – 1.8	0.9	0.5 – 3.3
		4	0.9	0.5 – 1.3	0.9	0.5 – 2.0	0.9	0.5 – 3.2
		5	0.8	0.6 – 1.2	0.9	0.6 – 1.7	0.9	0.6 – 3.4
		6	0.8	0.5 – 1.2	0.9	0.5 – 2.1	0.9	0.5 – 3.7
Direct Bilirub. (mg/dL)	0.1 – 0.4	Base	0.14	0.10 – 0.80	0.12	0.10 – 0.30	0.12	0.0 – 0.7
		2	0.13	0.10 – 0.40	0.13	0.10 – 0.40	0.13	0.1 – 0.5
		3	0.13	0.10 – 0.30	0.12	0.10 – 0.30	0.13	0.0 – 0.3
		4	0.15	0.10 – 0.40	0.13	0.0 – 0.40	0.13	0.0 – 0.9
		5	0.13	0.10 – 0.40	0.13	0.10 – 0.30	0.14	0.1 – 0.5
		6	0.14	0.0 – 0.30	0.13	0.10 – 0.50	0.12	0.1 – 0.2
GGT (IU/L)	2 - 24	Base	24.2	9 - 200	22.5	9 - 289	24.0	9 – 199
		2	23.8	9 - 205	20.0	7 - 247	21.1	9 – 136
		3	26.6	9 - 262	20.9	9 - 350	22.3	0 – 140
		4	27.4	9 - 338	21.4	9 - 343	21.7	9 – 107
		5	31.3	9 - 357	23.5	0 - 414	23.8	9 – 317
		6	29.1	9 - 302	23.2	9 - 331	22.5	9 - 176
Glucose (mg/dL)	74 - 106	Base	99.6	64 - 390	96.2	60 - 308	99	40 – 275
		2	103.2	59 - 436	102.8	67 - 346	104	56 – 297
		3	104.5	56 - 319	96.5	33 - 260	104	48 – 310
		4	106.0	64 - 351	97.9	64 - 395	105	59 – 281
		5	105.3	65 - 322	94.9	37 - 256	105	18 – 284
		6	98.2	69 - 291	97.1	50 - 242	105	58 - 288
Magnesium (mg/dL)	1.6 – 2.6	Base	2.13	1.5 – 2.6	2.15	1.8 – 2.7	2.2	1.0 – 3.1
		2	2.04	1.5 – 2.5	2.09	1.4 – 2.5	2.1	0.2 – 2.7
		3	2.08	1.6 – 2.7	2.09	1.6 – 2.4	2.1	0.1 – 2.7

Table 10.5a: Chemistries - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3

Laboratory Assessment (normal range)	Normal Range	Lab Visit*	851-CR1 Placebo		851-CR1 MiraLax		851-CR3 MiraLax	
			Mean	Range	Mean	Range	Mean	Range
		4	2.09	1.6 – 2.4	2.09	1.7 – 2.4	2.1	0.2 – 2.6
		5	2.11	1.8 – 2.4	2.09	1.6 – 2.4	2.0	0.2 – 2.6
		6	2.07	1.7 – 2.5	2.08	1.8 – 2.6	2.1	1.7 – 2.7
Phosphate (mg/dL)	2.7 – 4.5 2.7 – 4.5	Base	3.81	2.7 – 5.5	3.85	2.3 – 5.5	3.8	2.1 – 5.2
		2	3.84	2.3 – 5.5	3.86	2.6 – 6.3	3.7	2.1 – 5.2
		3	3.78	2.4 – 4.9	3.81	2.3 – 5.2	3.7	2.2 – 5.6
		4	3.83	2.9 – 4.9	3.87	2.3 – 5.9	3.7	2.1 – 5.2
		5	3.79	2.7 – 5.0	3.87	2.4 – 6.3	3.8	2.7 – 5.3
		6	3.83	2.9 – 4.7	3.85	2.2 – 5.4	3.8	2.3 – 5.6
Potassium (mEq/dL)	3.5 – 5.1	Base	4.22	3.3 – 5.9	4.25	3.1 – 5.9	4.26	3.2 – 5.7
		2	4.17	3.2 – 7.6	4.25	3.3 – 5.6	4.37	3.2 – 26.4**
		3	4.16	2.7 – 5.7	4.25	3.2 – 5.2	4.70	3.2 – 32.4**
		4	4.17	3.2 – 5.7	4.29	3.4 – 5.7	4.62	3.5 – 31.0**
		5	4.21	3.0 5.9	4.28	3.5 – 5.9	4.58	3.2 – 27.8**
		6	4.22	3.4 – 5.3	4.29	3.3 – 5.6	4.26	3.3 – 5.7
Sodium (mEq/dL)	136 - 145	Base	138.9	130 - 144	138.3	129 - 146	139	130 – 147
		2	138.6	130 - 151	138.3	129 - 144	139	130 – 150
		3	138.5	131 - 145	138.2	130 - 156	139	132 – 150
		4	138.7	132 - 143	138.0	128 - 145	138	131 – 146
		5	138.9	133 - 145	138.6	132 - 145	138	126 – 146
		6	138.9	133 - 143	138.9	129 - 143	139	130 - 146
Total Bilirubin (mg/dL)	0.3 – 1.2	Base	0.65	0.1 – 1.7	0.65	0.1 – 1.8	0.63	0.1 – 2.9
		2	0.65	0.1 – 1.4	0.69	0.2 – 1.5	0.63	0.2 – 1.6
		3	0.69	0.3 – 1.3	0.72	0.3 – 2.1	0.67	0.2 – 1.5
		4	0.71	0.2 – 1.4	0.70	0.2 – 1.6	0.63	0.2 – 1.4
		5	0.71	0.3 – 1.3	0.72	0.2 – 2.4	0.71	0.2 – 1.8
		6	0.70	0.3 – 1.5	0.68	0.2 – 2.0	0.71	0.2 – 1.5
Total Protein	6.0 – 8.0	Base	6.9	5.9 – 7.9	6.9	5.8 – 8.4	7.0	5.9 – 8.5
		2	6.7	5.8 – 7.8	6.7	5.6 – 8.2	6.8	5.5 – 8.9
		3	6.8	6.0 – 7.6	6.8	5.7 – 8.6	6.8	5.7 – 8.3

Table 10.5a: Chemistries - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3								
Laboratory Assessment (normal range)	**Normal Range**	**Lab Visit***	**851-CR1 Placebo**		**851-CR1 MiraLax**		**851-CR3 MiraLax**	
			Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
(g/dL)		4	6.9	5.9 – 7.7	6.8	5.7 – 8.1	6.8	5.2 – 8.2
		5	6.8	6.0 – 7.7	6.8	5.5 – 8.3	6.8	5.2 – 8.4
		6	6.8	5.8 – 7.6	6.8	5.7 – 7.9	6.9	4.7 – 8.9
Uric Acid (mg/dL)	2.6 – 6.0	Base	4.63	1.9 – 8.5	4.46	2.4 – 9.2	5.0	2.0 – 9.2
		2	4.65	3.0 – 8.7	4.57	2.5 – 8.5	5.0	1.9 – 9.5
		3	4.72	2.0 – 9.1	4.61	2.3 – 8.2	4.9	2.2 – 9.0
		4	4.89	3.1 – 8.3	4.56	2.4 – 8.9	5.0	2.7 – 8.7
		5	4.80	2.8 – 8.8	4.52	2.3 – 8.2	5.2	2.6 – 9.9
		6	4.92	2.9 – 8.6	4.50	2.2 – 9.3	5.1	2.8 – 9.4

*Lab visit denotes a study visit where blood and urine were collected. For Study 51-CR3, the lab visit correlates with the study visit but the tables exclude data from visit 7. The lab value ranges for visit 7 were very similar to those at visit 6.
**Median serum potassium level = 4.2 for all 4 visits. Maximum values probably due to severe hemolysis in a small number of blood samples. These serum potassium levels would be incompatible with life.

Table 10.5b: Hematology/ Urinalysis - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3								
Laboratory Assessment	**Normal Range**	**Lab Visit***	**851-CR1 Placebo**		**851-CR1 MiraLax**		**851-CR3 MiraLax**	
			Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
WBC ($10^3/\mu L$)	4.5 – 11.0	Base	6.58	3.7 – 11.3	6.40	3.1 – 12.3	6.7	2.5 – 17.5
		2	6.39	3.9 – 11.5	6.03	3.0 – 12.4	6.4	2.6 – 14.5
		3	6.36	2.9 – 14.3	6.24	3.3 – 13.1	6.4	2.2 – 16.4
		4	6.42	3.5 – 11.9	6.27	3.4 – 12.5	6.5	2.4 – 14.7
		5	6.67	2.0 – 20.5	6.06	3.7 – 10.1	6.5	2.8 – 14.4
		6	6.40	2.5 – 12.4	6.24	3.2 – 14.7	6.5	2.5 – 13.5
Hematocrit (%)	35.0 – 47.0	Base	40.2	31.7 – 52.7	40.1	32.4 – 50.3	40.6	28.5 – 51.7
		2	39.2	31.3 – 48.6	39.4	28.3 – 47.4	39.8	27.1 – 51.1
		3	39.8	29.5 – 49.5	39.7	29.1 – 48.6	39.5	25.1 – 53.3

Table 10.5b: Hematology/ Urinalysis - mean values and ranges for subjects on MiraLax or placebo in 851-CR1 And 851-CR3

Laboratory Assessment	Normal Range	Lab Visit*	851-CR1 Placebo		851-CR1 MiraLax		851-CR3 MiraLax	
			Mean	Range	Mean	Range	Mean	Range
		4	40.0	27.5 – 51.4	39.7	32.7 – 46.8	39.6	30.8 – 48.5
		5	39.9	33.2 – 50.6	39.6	33.0 – 47.3	39.7	30.3 – 51.3
		6	39.8	32.7 – 51.3	39.3	29.3 – 46.3	39.8	29.2 – 48.3
Hemoglobin (g/dL)	11.7 – 16.0	Base	13.6	10.4 – 17.5	13.6	10.4 – 17.1	13.6	8.8 – 17.2
		2	13.2	10.1 – 16.1	13.4	9.3 – 16.4	13.4	8.8 – 17.0
		3	13.4	9.5 – 16.8	13.5	9.5 – 16.3	13.3	8.4 – 17.8
		4	13.5	8.8 – 17.1	13.5	11.1 – 16.1	13.3	10.2 – 16.4
		5	13.5	11.3 – 17.1	13.5	11.1 – 16.4	13.4	9.9 – 16.9
		6	13.5	11.1 – 16.9	13.4	10.0 – 15.6	13.5	9.4 – 16.6
Platelets ($10^3/\mu L$)	150 – 400	Base	269	131 - 517	266	137 - 519	259	15 – 586
		2	273	138 - 542	261	125 - 533	267	129 – 541
		3	282	147 - 517	262	124 - 501	265	115 – 846
		4	281	139 - 568	261	134 - 518	266	121 – 524
		5	292	124 - 815	259	122 - 509	262	111 – 540
		6	271	126 - 462	254	132 - 378	261	108 – 456
Urine specific gravity	1.002 – 1.030	Base	1.02	1.02 – 1.03	1.02	1.01 – 1.03	1.02	1.01 – 1.03
		2	1.02	1.02 – 1.03	1.02	1.01 – 1.03	1.02	1.01 – 1.03
		3	1.02	1.02 – 1.03	1.02	1.01 – 1.03	1.02	1.01 – 1.03
		4	1.02	1.02 – 1.03	1.02	1.01 – 1.03	1.02	1.01 – 1.03
		5	1.02	1.01 – 1.03	1.02	1.01 – 1.03	1.02	1.01 – 1.03
		6	1.02	1.02 – 1.03	1.02	1.02 – 1.03	1.02	1.01 – 1.03

*Lab visit denotes a study visit where blood and urine were collected. For Study 851-CR3, the lab visit correlates with the study visit but the tables exclude data from visit 7. The lab value ranges for visit 7 were very similar to those at visit 6

10.6 Line Listing of Laboratory Abnormalities From Studies 851-CR1 and 851-CR3

Study 851-CR1:

Laboratory Abnormalities: 2.5 times Upper or Lower Limit of Normal
MiraLAX Patients

Site	Pt	Measure	Visit	Value	Comment
101	001	Triglycerides	1,5,7,8	>521	Baseline and other visits high. NCS per PI. History of Hypercholesterolemia.
112	019	GGT	All	>195	Baseline high. Visits 1,3 CS per PI. Adverse event reported.
112	019	Triglycerides	4	584	Baseline and other visits high. Visits 1,3,4 CS per PI. History of obesity.
112	021	TSH	8	0.12	Visit 1 normal. Visit 8 CS per PI. History of Hypothyroidism.
114	004	Glucose	5	395	Baseline and other visits high. NCS per PI. History of Diabetes.
117	005	Creatine Kinase	1	624	Baseline and Visits 3,5 high, other visits normal. NCS per PI.
117	008	Glucose	1	308	Baseline and Visits 3 and 8 high. Visit 3 CS per PI. History of Diabetes.
119	006	GGT	All	>107	Baseline high. Visit 6 CS per PI. Adverse event reported.
122	013	Bilirubin	1	0.1	Other visits normal. NCS per PI.
124	001	Bilirubin	7	0	Other visits normal. NCS per PI.
124	005	GGT	1,8	>280	Baseline high. NCS per PI.
129	002	ALT	7	137	Visit 4 high. Visits 7 and unscheduled samples CS per PI. Visit 8 normal. Adverse event reported.
129	002	GGT	4	98	Baseline and Visits 3, 5, 6, 7, 8 high. NCS per PI.
129	003	GGT	6	0	Other visits normal. NCS per PI.
130	001	Bilirubin	8	0.1	Other visits normal. NCS per PI.
131	010	Creatine Kinase	1	1770	Baseline high. Visit 1 repeat sample normal. Other visits normal.
132	003	Glucose	3,5	>297	Baseline and visit 8 high. NCS per PI. History of Diabetes.
136	003	Amylase	8	14	Baseline and other visits low. NCS per PI.
141	009	ALT	1	103	Baseline and other visits high. NCS per PI.
144	004	Bilirubin	5	0	Other visit normal. NCS per PI.
144	014	Bilirubin	8	0.1	Other visits normal. NCS per PI.
145	012	Amylase	1,4,5,8	>337	Baseline and other visits high. History of Fibromyalgia.
149	019	GGT	1,4,5,6,7,8	>83	Baseline and other visits high. NCS per PI.

Legend

CS: Clinically Significant
NCS: Not Clinically Significant
High / Low: outside of normal range

851-CR1 (cont.)

Laboratory Abnormalities: 2.5 times Upper or Lower Limit of Normal
Placebo Patients

Site	Pt	Measure	Visit	Value	Comment
102	005	GGT	1,3,4,5	>93	Baseline and other visits high. NCS per PI.
104	001	ALT	1	104	Baseline high. NCS per PI.
105	002	Glucose	1,4,5,6,7,8	>291	Baseline and other visits high. History of Diabetes.
110	015	CK	3	994	Baseline high. Next visit (visit 4) was normal.
117	6	Bilirubin	3	0.1	Visit 5 and 8 low. NCS per PI.
118	006	GGT	All	>200	Baseline high. Visits 6,7,8 CS per PI. History of increased GGT.
119	002	ALT	1	77	Baseline and other visit high. NCS per PI.
119	002	GGT	1,8	>91	Baseline high. NCS per PI.
121	002	Bilirubin	1	0.1	Baseline and Visit 4 low. Visits 3,5 normal.
121	012	ALT	6	110	Visit 5 and 8 high. Visit 6 CS per PI. Adverse event reported.
128	002	ALT	8	137	Baseline high, other visits normal. NCS per PI. Adverse event reported.
128	002	GGT	8	485	Baseline and visits 3 and 4 high. NCS per PI. Adverse event reported.
128	002	Glucose	8	435	Visits 3, 4 high. NCS per PI (non fasting).
134	012	ALP	6	264	Visit 5, 8 high. Adverse event reported.
134	012	GGT	6	73	Visit 4, 5 high. Next visit (visit 8) was normal. Adverse event reported.
136	012	Glucose	5,8	>288	Baseline and other visits high. NCS per PI. History of diabetes.
149	021	Glucose	1,3,8	>353	Baseline high. History of diabetes.

Legend

CS: Clinically Significant
NCS: Not Clinically Significant
High / Low: outside of normal range

Study 851-CR3:

Laboratory Abnormalities: 2.5 times Upper / Lower Limit of Normal
MiraLAX

Site	Pt	Measure	Visit	Value	Comment
101	050	GGT	1	99	Baseline and visits 3,4,6 high. NCS per PI.
102	001	Creatine Kinase	4	614	Baseline and visits 2, 3, 5, unscheduled high. Visit 4 CS per PI. Repeat test near normal; NCS.
102	254	Potassium	3	27.1	Other visits normal. Repeat test was normal. Probable lab error.
102	254	Magnesium	3	0.2	Other visits normal. Repeat test was normal. Probable lab error.
103	097	AST	1	99	Baseline high. Visits 2,3,6 normal. NCS per PI.
104	130	Triglycerides	3	712	Baseline and Visits 2,4,5 high. NCS per PI. History of hypercholesterolemia
105	105	Triglycerides	3	630	Baseline and Visit 2 high. Visits 4,5,6 normal. History of hyperlipidemia.
106	134	Direct Bilirubin	4	0	Baseline and other visits low. NCS per PI.
106	135	Direct Bilirubin	4	0	Visit 1,6 normal. NCS per PI.
106	135	Triglycerides	1,3	>508	Baseline and other visits high. History of hyperlipidemia. NCS per PI.
106	138	GGT	1	61	Baseline high. NCS per PI.
108	012	GGT	1	71	Baseline high. NCS per PI.
110	065	Potassium	5	27.3	Other visits normal. Repeat test was normal. Probable lab error.
110	065	Magnesium	5	0.3	Other visits normal. Repeat test was normal. Probable lab error.
110	066	Glucose	5	18	Other visits normal. Probable lab error.
111	014	Direct Bilirubin	4	0	Visit 6 normal. NCS per PI.
111	016	Triglycerides	2,3,4,6	>594	Baseline and other visits high. NCS per PI.
111	018	ALT	1	119	Baseline and Visit 2 high. NCS per PI.
111	018	GGT	1	92	Baseline and Visit 2 high. NCS per PI.
112	119	Triglycerides	5	950	Visits 4, 6 high. History of high cholesterol. Visit 5 CS per PI.
113	142	ALT	5	207	Repeat test was normal. Other visits normal. NCS per PI.
113	142	AST	5	152	Repeat test was normal. Other visits normal. NCS per PI.
113	142	GGT	5 and unscheduled	>126	Baseline and other visits high. NCS per PI. Repeat test (unscheduled) reduced but high.

Legend

CS: Clinically Significant
NCS: Not Clinically Significant
High / Low: outside of normal range

(cont.)

851-CR3 (cont.)

Laboratory Abnormalities: 2.5 times Upper / Lower Limit of Normal
MiraLAX

Site	Pt	Measure	Visit	Value	Comment
113	143	Creatine Kinase	3	1694	Other visits normal. Visit 3 CS per PI. At that time, adverse event FLU reported.
113	144	Magnesium	5	0.2	Other visits normal. Visit 6 normal. NCS per PI.
113	144	Potassium	5	20.3	Other visits normal. Visit 6 normal. NCS per PI. Likely hemolyzed.
114	213	GGT	1,3	>61	Baseline and other visits high. History of polycystic Liver disease, NCS per PI.
115	293	Platelets	1	15	Baseline high. Repeat test was normal. Other visits normal.
115	293	GGT	All	>98	Baseline high. NCS per PI.
116	019	Creatinine	3,5,6	>3.3	Baseline and other visits high. NCS per PI.
116	023	Magnesium	5	0.2	Other visits normal. NCS per PI. Repeat test was normal. Probable lab error.
116	023	Potassium	5	27.8	Visit 3 high. NCS per PI. Repeat test was normal. Probable lab error.
117	092	Direct Bilirubin	1	0	Baseline high. NCS per PI.
117	094	GGT	1	93	Baseline high. NCS per PI.
117	095	GGT	2	86	Baseline and Visit 3 high. NCS per PI. Following visits were normal.
119	262	GGT	1,3,4,6, unscheduled	>78	Baseline and Visit 5 high. Visit 1 CS per PI. History of hyperlipidemia. Adverse Event reported.
120	175	GGT	5	69	Baseline high. All visits high.
120	177	ALT	5	143	Baseline high. All visits high. History of Hypothyroid.
120	177	AST	5	137	Baseline high. All visits high. History of Hypothyroid.
120	177	GGT	3	76	Baseline high. All visits high. History of Hypothyroid.
121	159	GGT	All	>68	Baseline high. All visits high. History of diabetes.
121	160	Creatine Kinase	3	592	Other visits normal. Following visits were normal. NCS per PI.
121	162	Magnesium	3	0.1	Other visits normal. Repeat test done was normal. Probable lab error.
121	162	Potassium	3	25.1	Other visits normal. Repeat test done was normal. Probable lab error.
122	026	GGT	1,2,3,4,6	>67	Baseline and Visit 5 high. NCS per PI.

Legend

CS: Clinically Significant
NCS: Not Clinically Significant
High / Low: outside of normal range

(cont).

851-CR3 (cont.)

Laboratory Abnormalities: 2.5 times Upper / Lower Limit of Normal
MiraLAX

Site	Pt	Measure	Visit	Value	Comment
123	218	Magnesium	2	0.4	Subject lost to follow up. Probable lab error.
123	218	Potassium	2	15.1	Subject lost to follow up. Probable lab error.
124	302	Glucose	5	284	Baseline and Visits 2, 3, 4 high. NCS per PI. History of diabetes.
124	429	Glucose	6	272	Baseline and other visits high. History of diabetes. NCS per PI.
125	224	Amylase	4	345	Baseline and visits 2, 3, 6 high. History of diabetes.
125	224	Triglycerides	2,5,6	>623	Baseline and Visit 3 high. History of diabetes and Hypercholesterolemia. NCS per PI.
125	227	Creatine Kinase	1	1042	Baseline high. Following visit was normal. NCS per PI.
127	249	Creatine Kinase	1	936	Baseline high. History of coronary artery disease, transient ischemic attack and myocardial infarction. Visit 1 CS per PI. Repeat test done was normal.
128	244	Magnesium	4	0.2	Other visits normal. NCS per PI. Incorrect specimen type. Probable lab error.
128	244	GGT	6	103	Baseline and other visits high. NCS per PI (pre-existing condition).
128	244	Potassium	4	31	Visit 2 high. NCS per PI. Following visits were normal. Incorrect specimen type. Probable lab error.
130	173	GGT	3	140	Other visits normal. NCS per PI.
134	145	Triglycerides	3	710	Baseline high. Other visits normal. History of hypercholesterolemia. NCS per PI.
135	195	AST	5	107	Visit 6 high. NCS per PI.
135	195	GGT	6	83	Visit 5 high. NCS per PI.
135	417	GGT	1,6	>63	Baseline and other visits high. NCS per PI.
136	230	Potassium	4	25.9	Other visits normal. Visits 5,6 normal. Probable lab error.
136	431	Magnesium	2	0.2	Other visits normal. Repeat test was normal. Probable lab error.
136	431	Potassium	2	26.4	Other visits normal. Repeat test was normal. Probable lab error.

Legend

CS: Clinically Significant
NCS: Not Clinically Significant
High / Low: outside of normal range

(cont.)

851-CR3 (cont.)

Laboratory Abnormalities: 2.5 times Upper / Lower Limit of Normal
MiraLAX

Site	Pt	Measure	Visit	Value	Comment
137	031	Creatine Kinase	6	1038	Other visits normal. Repeat test was normal.
139	187	Glucose	1	275	Baseline and Visit 2 high. NCS per PI. History of diabetes.
139	188	TSH	1	0.1	Baseline high. Following visit (9 days later) was normal.
141	042	GGT	4,5	>91	Other visits normal. NCS per PI.
144	165	GGT	3	0	Other visits normal, NCS per PI.
145	271	GGT	1	77	Baseline high. NCS per PI.
146	043	Total Bilirubin	6	0.1	Other visits normal. NCS per PI.
146	047	Triglycerides	6	517	Baseline high. History of hypercholesterolemia. NCS per PI.
147	085	Magnesium	4	0.2	Other visits normal. NCS per PI. History of diabetes. Probable lab error.
147	085	GGT	6	67	Baseline and other visits high. History of diabetes. NCS per PI.
147	085	Potassium	3,4	>25.6	Other visits normal. NCS per PI. History of diabetes. Probable lab error.
147	086	Creatine Kinase	1,2	>646	Baseline high. NCS per PI.
147	090	Magnesium	3	0.1	Other visits normal. Visit 4 normal. NCS per PI. Probable lab error.
147	090	Potassium	3	32.4	Other visits normal. Visit 4 normal. Probable lab error.
148	004	Glucose	2,3,6	>288	Baseline and other visits high. History of diabetes. NCS per PI.
148	181	Direct Bilirubin	4	0	Other visits normal. NCS per PI.
148	185	ALT	2	113	Visits 3, 4, 6 high. Visit 2 CS per PI. Adverse event reported.
148	186	GGT	1,2	>76	Baseline and other visits high. NCS per PI.
149	278	Direct Bilirubin	3	0	NCS per PI.
149	420	ALT	3	0	Other visits normal. NCS per PI.
149	420	Direct Bilirubin	3	0	NCS per PI.
150	122	Total Bilirubin	1	0.1	Baseline high. Other visits normal. NCS per PI.
150	125	GGT	All	>77	Baseline high. History of Helicobacter Pilori. NCS per PI.

Legend

CS: Clinically Significant
NCS: Not Clinically Significant
High / Low: outside of normal range

2 Page(s) Withheld

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✓ Draft Labeling

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