CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-015

MEDICAL REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 10/05/06

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: Deputy Division Director Approvable Comments
NDA 22-015

APPLICANT: Braintree Laboratories, Inc.

DRUG: MiraLax® Oral Powder for Solution
(Polyethylene Glycol 3350) mg)

DIVISION RECOMMENDATION:
The division recommends approval of the prescription to OTC switch proposed in the NDA 22-015. This switch would provide for the use of MiraLax for 7 days for the relief of occasional constipation. We have no substantial safety concerns at this time. We agree with the recommendation that OTC MiraLax is appropriate for a 7 day course.

The Division of Gastrointestinal Products has reviewed this supplement in concert with the review by the Division of Nonprescription Clinical Evaluation. We were tasked with review of the efficacy information submitted in this supplement. We have participated in all of the labeling negotiations with the sponsor. We are in agreement with the direction that DNCE is preceding regarding the final Over the Counter labeling.

I have reviewed the Action Package including Dr. Andrea Leonard-Seigal's Division Director Review. There are no unresolved issues at this time except the receipt of the final draft label by DNCE. I agree that the pediatric studies be deferred for 10 years at this time. [redacted] At this time, the DGP does not recommend pediatric patients be prescribed MiraLax or that the OTC switch include pediatric patients. This has been discussed and agreed upon by DNCE.

The clinical studies submitted [redacted] for the prescription product; however, the sponsor has chosen to utilize this data for a switch from prescription drug to OTC product with a 7 day course of treatment. [redacted]

I agree with Dr. Feibus' assessment of safety and acknowledge the pharmacology/toxicology reviewers statement that adequate pre-clinical studies have

been performed and they support the OTC switch. There are no significant safety concerns at this time in the adult population.

I agree with the division recommendation that it is appropriate to proceed with a prescription to OTC switch for MiraLax.

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/s/

Joyce Korvick
10/6/2006 09:26:44 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: 8/14/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 22-015

APPLICANT: Braintree Laboratories, Inc.

DRUG: MiraLAX (polyethylene glycol 3350 powder laxative)
Rx-to-OTC Switch

RECOMMENDATION:

I recommend that NDA 22-015, MiraLAX (polyethylene glycol 3350 powder laxative) Rx-to-OTC Switch, be approved for relieving occasional constipation in the adult population at a dose of 17 grams of powder per day in solution [redacted]. For approval of this application, the sponsor needs to incorporate the Division's recommendations into the MiraLAX label and agrees to the required post-marketing commitment.

The sponsor requested a deferral of all pediatric age groups (birth to 16 years) for OTC use. [redacted] I recommend that the deferral request be granted for all pediatric age groups (birth to 16 years) for OTC use, until safety and effectiveness have been established in Rx pediatric population. The sponsor should provide a pediatric development plan for the OTC use.

I. BACKGROUND:

Constipation, generally defined as infrequent and difficult passage of stool, is one of the most common disorders suffered by Americans. In the United States, it results in more than 2.5 million visits to physicians and 92,000 hospitalizations annually. Factors

contributing to the development of constipation can include inadequate fiber in the diet, lack of exercise, neurological and systemic disorders and problems with colonic, rectal, and/or intestinal function. Other contributing factors can include side effects from medication, particularly narcotic analgesics, antidepressants, antacids, antispasmodics, anticholinergics, and blood pressure medications.

The treatment of constipation depends on the cause, severity, and duration of symptoms; however, in most cases dietary (increasing dietary fiber to 20 – 35 grams per day) and lifestyle changes (increasing daily fluid intake and engaging in daily exercise) can help relieve constipation. For patients who have made lifestyle modifications and are still constipated, laxatives are the most commonly prescribed pharmacological interventions, of which there are four main types (bulk, osmotic, stimulant, and softener).

Polyethylene glycol (PEG) 3350 is a mixture of non-absorbable, non-metabolized polymers of mean molecular weight 3350 (±10%) that act as pure osmotic agents. PEG has been available in prescription form as MiraLAX™ (Polyethylene Glycol 3350, NF Powder for Solution) since February 1999. Prescription MiraLAX™ at a dose of 17 grams of powder per day in solution is indicated for the treatment of occasional constipation in the adult population, to be used for 2 weeks or less or as directed by a physician.

In this New Drug Application, the sponsor is proposing that prescription MiraLAX™ is an excellent drug candidate to switch to over-the-counter. Dr. Kristen Buck from the Division of Gastroenterology Products conducted efficacy evaluation of the NDA and Dr. Karen Feibus from the Division of Non-Prescription Drug Products will provide safety assessment for this submission.

II. CLINICAL EFFICACY REVIEW SUMMARY AND COMMENTARY:

MiraLAX depends upon the osmotic effect of PEG-3350 to increase the water content of the stool with a resulting increase in stool volume. It is virtually non-absorbed and metabolism is not required for its action. Two clinical studies performed in support of the original NDA (NDA 20-698, approved February 18, 1999) established the safety and efficacy of MiraLAX for up to two weeks of therapy (package insert for prescription MiraLax).

This application includes three new clinical studies; 851-CR1, 851-ZCC and 851-CR3.

Study 851-CR1 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center trial comparing MiraLAX 17 grams to placebo in daily dosing. Study 851-CR1 was a six month efficacy and safety study which included 304 intent-to-treat patients of which 75 were 65 years of age or older.

Study 851-ZCC was a randomized, open-label, parallel, multi-center trial comparing MiraLAX 17 grams daily dosing to Zelnorm 6 mg twice daily dosing. Study 851-ZCC was a one month safety and efficacy study.

Study 851-CR3 was a Phase 4, open-label, extended use, multi-center, single treatment study of MiraLAX 17 grams per day. Study 851-CR3 was a twelve month safety study of chronic MiraLAX use which included 311 intent-to-treat patients, of which 117 were 65 years of age and older.

All three studies utilized a modified ROME constipation definition for enrollment:

A. Satisfactory stools less frequent than 3 per week, and
B. 1 or more of the following additional ROME based criteria
   a. Straining in more than 25% of defecations
   b. Lumpy or hard stools in more than 25% of defecations
   c. Sensation of incomplete evacuation in more than 25% of defecations

All three clinical studies (851-CR1, 851-CR3, and 851-ZCC) enrolled constipated, yet otherwise healthy male and female adult outpatients. Study Demographics were summarized in Table 1 below.

Table 1: Study Demographics

Variable	851-CR1	851-CR3	851-ZCC
Age (years)[1]			
Mean (SD)	53.5 (14.9)	56.9 (16.4)	46.5 (14.5)
≥65	75 (25%)	117 (38%)	31 (13%)
n	304	311	237
Gender: n (%)			
Female	258 (85)	248 (80)	213 (90)
Male	46 (15)	63 (20)	24 (10)
Race: n (%)			
Caucasian	255 (84)	248 (80)	151 (63.7)
A. American	39 (12.8)	49 (16)	57 (24.1)
Other	5 (1.6)	4 (1)	10 (4.2)
Missing	5 (1.6)	10 (3)	19 (8.0)
Weight (kg)			
Mean (SD)	74.8 (16.0)	77.3 (17.6)	76.4 (20.4)
Constipation Hx.			
(yrs) (SD)	23.1 (18.9)	17.9 (19.1)	17.5 (16.3)

1. Age is calculated using date of birth and screening visit (Visit 1) date.
SD = Standard deviation; kg = kilograms; A. American = African American

Due to the differing objectives and designs of the studies the efficacy endpoints used in each study were not the same. For clinical efficacy results, I will summarize the results from Study 851-CR1 and 851-ZCC in the following section. Study 851-CR3 was a twelve month safety study of chronic MiraLAX use which will be evaluated by Dr. Karen Feibus in her review.

Study 851-CR1

The primary efficacy endpoint comparing MiraLAX to placebo was based on a binary outcome of overall treatment success (responder) as defined below.

A. Satisfactory stools greater or equal to 3 per week, and
B. 1 or fewer of the following additional ROME based criteria
   a. Straining in more than 25% of defecations
   b. Lumpy or hard stools in more than 25% of defecations
   c. Sensation of incomplete evacuation in more than 25% of defecations

Primary Efficacy Responder Analysis: Number of Successfully Treated Patients for Study 851-CR1 was summarized in Table 2 below.

Table 2: Primary Efficacy Responder Analysis: Number of Successfully Treated Patients in Study 851-CR1

Responder	MiraLAX n (%)	Placebo n (%)	95% CI[1]	P[2]	Δ MiraLAX and Placebo responder %
All Patients (n) Yes No	204 106 **(52)** 98 (48)	100 11 **(11)** 89 (89)	31.8, 50.2	<0.001	41%
Elderly (≥ 65 y) Yes No	51 30 **(59)** 21 (41)	24 3 **(13)** 21 (87)	27.4, 65.2	<0.001	46%
Non-Elderly (<65 y) Yes No	153 76 **(50)** 77 (50)	76 8 **(11)** 68 (89)	28.6, 49.7	<0.001	39%
Males Yes No	29 13 **(45)** 16 (55)	17 1 **(6)** 16 (94)	17.7, 60.2	0.007	39%
Females Yes No	175 93 **(53)** 82 (47)	83 10 **(12)** 73 (88)	30.9, 51.3	<0.001	41%
Caucasian Yes No	172 89 **(52)** 83 (48)	88 10 **(11)** 78 (89)	30.4, 50.4	<0.001	41%
Non-Caucasian Yes No	32 17 **(53)** 15 (47)	12 1 **(8)** 11(92)	21.5, 68.1	0.014	45%

1. Confidence interval (CI) for the difference between MiraLAX and placebo is from a Cochran-Mantel-Haenzsel test or Fisher's Exact test (for race).
2. P-value for the difference between MiraLAX and placebo is from a pooled site stratified Cochran-Mantel- Haenzsel test or Fisher's Exact test (for race).

The primary responder analysis for the ITT population showed a highly statistically significant difference (41%; $p<0.001$) in successful patient treatment response between MiraLAX (52%) and placebo (11%) over the six month study period. The elderly subpopulation demonstrated similar statistically significant results in favor of MiraLAX with a 46% ($p<0.001$) difference in treatment response between MiraLAX (59%) and placebo (13%). Gender and race did not seem to influence the efficacy variables. Both males and females significantly improved on MiraLAX relative to placebo, similar to the general study population. The difference for males was (39%, $p = 0.007$) and the difference for females was (41%, $p <0.001$). Caucasian as well as Non-Caucasian subjects significantly improved on MiraLAX relative to placebo with response differences of (41%, $p <0.001$) and (45%, $p = 0.014$), respectively. This study indicated that MiraLAX is effective over placebo in the treatment of constipation for a period of 6 months. Statistically significant differences and clinically meaningful differences were also observed when various patient subgroups were analyzed (age, gender, and race).

There were no substantial changes in mean dose for either MiraLAX or placebo over the course of the study. Most patients (80.3%) that did not use rescue medication experienced a bowel movement within one to three days of starting therapy. In those patients who did not use any rescue medication in the first treatment week, 46% at Day 1, 63% at Day 2 and 80% at Day 3 experienced a bowel movement.

Study 851-ZCC:

The primary efficacy variable for treatment response was assessed on the basis of binary outcome of overall treatment success (responder) or failure (non-responder) where:

1. Overall treatment success was defined as 0.50 or greater rate of successful treatment weeks to weeks of actual treatment.
2. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative:
    - Straining in more than 25% of defecations
    - Lumpy or hard stools in more than 25% of defecations
    - Sensation of incomplete evacuation in more than 25% of defecations
3. Patients who received fewer than 2 weeks of active treatment for any reason were classified as overall treatment failures.

The primary responder analysis for the intent-to-treat (ITT) population in study 851-ZCC was summarized in Table 3 below.

Table 3: Primary Efficacy Responder Analysis: Number of Successfully Treated Patients at 1 month in Study 851-ZCC

Responder	MiraLAX n (%)	Zelnorm n (%)	95% CI[1]	p[2]	Δ MiraLAX and Zelnorm responder %
All Patients (n)	120	117			
Yes	60 (50.0)	36 (30.8)	7.0, 31.5	0.003	19.2 %
No	60 (50.0)	81 (69.2)			

1. (CI): Confidence interval; difference between MiraLAX and Zelnorm is from Cochran-Mantel-Haenzsel-Test.
2. P-value for the difference between MiraLAX and Placebo is from a pooled site stratified Cochran-Mantel-Haenzsel-test.

The primary responder analysis for the ITT population showed a statistically significant 19% difference (p=0.003) in successful patient treatment response favoring MiraLAX over Zelnorm. Thus, 50% of MiraLAX patients vs. 30.8% of Zelnorm patients were successfully treated over the 4 week study period. When analyzing only the non-elderly population for which Zelnorm is currently approved, the statistically significant effect persists (p=0.032), where 16% more MiraLAX patients were successfully treated (48% vs. 32%), MiraLAX vs. Zelnorm, respectively. This study demonstrates that at one month, MiraLAX has superior efficacy in the responder analysis to Zelnorm, an approved medicine for chronic idiopathic constipation.

Some of the results from the secondary efficacy analyses also revealed statistical significance showing MiraLAX superiority. A review of individual treatment weeks showed that when using the study definitions of successful treatment based on the primary endpoint definition, and the clinically accepted ROME Definition, statistical significance was reached in favor of MiraLAX at Week 2 and continued through Week 4. When the Super Efficacy Definition was applied (no ROME criteria; the complete absence of constipation symptoms), MiraLAX achieved statistically significant superiority in response at Weeks 3 and 4. A review of the individual ROME symptom criteria by week (mean number of successful weeks) shows that the two main factors contributing to the superior efficacy of MiraLAX are improved stool consistency (p=0.001) and straining (p=0.065). MiraLAX patients experienced a greater number of bowel movements (BMs) per week compared to Zelnorm (10.42 vs. 8.48, respectively, p=0.019) and most experienced a bowel movement within one to three days after starting treatment. In addition, BMs reported by the MiraLAX group were less lumpy/hard compared to those experienced by the Zelnorm group (31% difference, p=0.001). For detail efficacy evaluation, please see Dr. Kristen Buck's review dated July 26, 2006.

Given that the endpoint(s) in study 851-ZCC were not designed to capture "time to event" data or early efficacy data (i.e. days), the primary medical officer, Dr. Kristen Buck, extracted the weekly and daily bowel movement data from the sponsor's submitted efficacy as shown below, to determine MiraLAX's initial efficacy by week.

Table 4: Study 851-ZCC Satisfactory Stools/Day in Weeks 1 through 4 (means)

	Satisfactory STOOLS/DAY (mean)		
	MiraLAX	**Zelnorm**	**P-value**
Week 1	0.84	0.87	0.846
Week 2	1.16	0.92	**0.034**
Week 3	1.20	1.07	0.307
Week 4	1.35	0.98	**0.012**

Dr. Buck's table, taken from Module 5, Volume 9.2, section 14

As noted in Table 4 above, regardless of statistical significance, during all four weeks, both MiraLAX and Zelnorm were clinically effective at relieving constipation.

At week 1, the outcome for MiraLAX translated into a clinically meaningful outcome as such: MiraLAX subjects had a mean of 0.86 BMs/day which equals 5.9 BMs/week or 1 BM every 1.2 days.

At week 2, the outcome for MiraLAX translated into a clinically meaningful outcome as such: MiraLAX subjects had a mean of 1.16 BMs/day which equals 8.1 BMs/week or 1 BM every 0.86 days.

Overall, the above data essentially translates into patients on MiraLAX having less than three bowel movements per week to approximately one bowel movement per day by week 1 and 2. For detailed efficacy evaluation, please see Dr. Kristen Buck's review dated July 26, 2006.

In addition, another analysis indicated that in those patients that did not use any rescue medication in the first treatment week, 54% at Day 1, 78% at Day 2 and 90% at Day 3 experienced a bowel movement.

Study 851-ZCC excluded elderly and male patients due to the likelihood of Zelnorm labeling restrictions at that time. Therefore, subgroup analyses for age and genders were not performed.

Overall, while MiraLAX and Zelnorm are both approved for the treatment of constipation, this study demonstrated that MiraLAX is more effective than Zelnorm in treating constipation over a four week period.

Safety:

Dr. Karen Feibus in the Division of Non-Prescription Drug Products will provide safety assessment for this submission. Please see her review for details.

Pediatric Use:

MiraLAX™ prescription use in adult population was approved in February 1999. Prescription MiraLAX™ at a dose of 17 grams of powder per day in solution is indicated for the treatment of occasional constipation in the adult population, to be used for 2 weeks or less or as directed by a physician.

[redacted]

[redacted] The sponsor requested a deferral of all pediatric studies (birth to 16 years) to support the OTC MiraLAX NDA 22-015. I recommend that the deferral request be granted for all pediatric age groups (birth to 16 years) for OTC use, until safety and effectiveness have been established in Rx pediatric use. The sponsor should provide a pediatric development plan for the OTC use.

III. Labeling Recommendations:

I concur with Dr. Keith St. Amand's labeling recommendations listed in his review. The labeling recommendations are summarized as following:

[redacted]

- Under the section of Directions, [redacted] The use of "fill to top of white section in cap" is acceptable.

- The age range for children should be defined (≤ 16 gears) in the label. It should be noted that deferral request is granted for all pediatric age groups (birth to 16 years) for OTC use.

- [redacted]

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/s/

Ruyi He
8/14/2006 03:37:49 PM
MEDICAL OFFICER

MEDICAL OFFICER LABELING REVIEW

Application Type	NDA
Submission Number	22-015
Submission Code	000
Letter Date	06 December 2005
Stamp Date	08 December 2005
PDUFA Goal Date	06 October 2006
Labeling Reviewer Name	Keith B. St. Amand, MD
Labeling Review Assigned	31 July 2006
Review Completion Date	10 August 2006
Established Name	Polyethylene Glycol 3350 Powder Laxative
(Proposed) Trade Name	MiraLAX OTC
Therapeutic Class	Laxative
Applicant	Braintree Laboratories, Inc.
Priority Designation	Standard
Formulation	Oral powder for solution
Dosing Regimen	17 grams once daily
Indication	Occasional Constipation
Intended Population	Adult population

1. Background

Prescription MiraLAX was approved in February 1999 for the indication of treatment of occasional constipation at a dose of 17 grams of powder in solution given once daily for 2 weeks or less.

In this current NDA the sponsor is proposing a switch from prescription to OTC use. Dr. Kristen Buck was the primary medical officer for this NDA; for detailed evaluation of the product's efficacy please see her review dated July 26, 2006. I was assigned the labeling evaluation July 31st, 2006. In the following section, I will provide comments and recommendations regarding the MiraLAX OTC label.

2. Line-by-Line Labeling Review

Materials Reviewed: NDA 22-015 Module 1, Volume 1.1, Tab 1.3
(Proposed MiraLAX OTC label);
Prescription MiraLAX package insert;
Other OTC laxative product labels

2.1 Active ingredient

The sponsor proposed: "polyethylene glycol 3350, 17g [redacted] ... purpose=laxative"

Reviewer comments: The choice of [redacted] as a dose measurement is not acceptable and will result in inexact amounts of medication from dose to dose within the same patient. In addition, the interpretation of what constitutes [redacted] will vary from one patient to another. I recommend that [redacted] be deleted from this section.

2.2-Use

2.2.1-The sponsor proposed: "relieves occasional constipation"

Reviewer comments: The use of the term "occasional constipation" is somewhat confusing as constipation is typically either acute (i.e., caused by medications or dehydration) or chronic (from either functional or non-functional causes.) However, prescription MiraLAX was approved for the treatment of "occasional constipation" in its original NDA (NDA 20-698) approved 18 February 1999, so this language is acceptable.

There is some concern that this product could be used by patients in an attempt to treat non-functional constipation (i.e. that caused by hypothyroidism, neurologic problems, or other medications) but the *Warnings* section detailed below addresses this concern.

2.2.2- The sponsor proposed: "this product generally produces bowel movement in 1 to 3 days"

Reviewer comments: Current efficacy data as reviewed by Dr. Buck support this statement (see her review for details) but this statement should not be included in the "Use" section of the label. This information should be moved to the "When using this product" section.

2.3-Warnings

For detailed comments related to the Warnings section, please see the safety evaluation and labeling recommendations provided by Dr. Karen Feibus who is performing the safety review for this NDA. Some general comments from this reviewer are presented below.

2.3.1-The sponsor proposed: "Stop use and ask a doctor if… -you need to use MiraLAX laxative for longer than [redacted]

Reviewer comments: From an efficacy standpoint, this warning is acceptable since [redacted] course of therapy. For safety concerns related to this warning, please see Dr. Feibus's recommendations.

2.3.2-The sponsor proposed: "Stop use and ask a doctor if…- [redacted]

Reviewer comments: [redacted]

2.4-Directions

2.4.1-The sponsor proposed: "Adults= [redacted] (17 g) or fill to top of white section in cap, completely dissolve in 4 to 8 oz beverage and drink—once daily"

Reviewer comments: Please see earlier comments relating to the use of [redacted] That measurement should be deleted. The use of "fill to top of white section in cap" is acceptable.

2.4.2-The sponsor proposed: "Children= ask a doctor"

Reviewer comments: The age range for children should be defined (according to the clinical trial data.)

3. Additional Reviewer comments:

The sponsor has proposed [redacted] different package labels for this product: 7-dose, 14-dose, [redacted] as well as a 12-pack of single dose packets. According to the prescription package insert, MiraLAX is indicated for [redacted] less. Given the [redacted] treatment limitation for this product, it is not necessary for the packages to include more than a 14-day supply for OTC use. With this in mind, [redacted], but the other forms are acceptable as they will reinforce the need for consumers to consult their physicians after using the product for 2 weeks.

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/s/

Keith B St.Amand
8/11/2006 10:32:41 AM
MEDICAL OFFICER

Ruyi He
8/11/2006 10:45:55 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type: NDA
Submission Number: 22-015
Submission Code: 000

Letter Date: 2005-12-06
Stamp Date: 2005-12-08
PDUFA Goal Date: 2006-10-08

Reviewer Name: Karen B. Feibus, M.D.
Review Completion Date: 2006-08-09

Established Name: Polyethylene glycol 3350
(Proposed) Trade Name: MiraLax OTC
Therapeutic Class: Laxative
Applicant: Braintree Laboratories, Inc.

Priority Designation: S

Formulation: NF Powder for Solution
Dosing Regimen: 17g dissolved in liquid for oral ingestion once a day [redacted]
Indication: Occasional constipation
Intended Population: Individuals age [redacted] and older with occasional constipation

Table of Contents

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a safety perspective, this application is approvable pending changes to the proposed OTC label. If there are no new safety signals noted upon review of the required safety update and more detailed postmarketing information requested, then this application should be approved with a seven day labeled duration of use.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Routine yearly and periodic adverse event reporting.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

Pediatric studies and a pediatric development plan for children ages two years and above is deferred until a decision is made about submitting additional pediatric data under a Pediatric Written Request to NDA 20-698.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Braintree Laboratories, Inc. submitted NDA 22-015 to support the safety and efficacy of nonprescription use of MiraLax 17 g/day [redacted] for the treatment of occasional constipation in adults. The sponsor submitted three clinical efficacy and/or safety studies to support their application:

- **851-CR1:**
  A randomized, double-blind, placebo-controlled, multicenter study of 304 subjects comparing six months of treatment with PEG 3350 17 g/day to daily treatment with a matched placebo.

- **851-CR3:**
  An open-label, long term, multicenter study of 311 subjects using PEG 3350 17 g/day for 12 months.

- **851-ZCC:**
  An open-label, randomized, parallel arm, multicenter study of normal constipated adult patients randomized to treatment with either 17 g/day PEG 3350 or Zelnorm (tegaserod maleate) for 28 day. Shortly after enrollment began, a protocol amendment stopped enrollment of all males and females over age 65 years.

  Eligible subjects were constipated adults with no documented organic cause for constipation who met protocol-specified modified Rome criteria for constipation:

  - Less than three satisfactory stools per week (on average over the 14 day period)
  - One or more of the following additional Rome-based criteria in more than 25% of defecations: straining, lumpy or hard stools, or sensation of incomplete evacuation.

  For study 851-CR1 study candidates needed to meet these constipation criteria during a 14 day observation period prior to randomization.

  Study candidates were excluded for: heme positive stool; uncorrected hypo- or hyper-thyroidism; suspected gastrointestinal perforation or obstruction; known organic causes of constipation; history of gastric retention, inflammatory bowel disease, bowel resection, or colostomy; irritable bowel syndrome (by diagnostic criteria); use of medications that affect bowel habits; pregnancy or breastfeeding; and known allergy to PEG and/or corn and/or ingredients in Zelnorm (depending on the study).

  In study 851-CR3, all subjects were treated with Miralax. In study 851-CR1, subjects who met study criteria were randomized 2:1 to PEG or placebo treatment. In study

851-ZCC, subjects were randomized 1:1 to PEG or Zelnorm. For both controlled trials, subjects used an interactive voice response system (IVRS) to complete daily bowel movement (BM) reports. Subjects returned to the study site monthly. For study 851-CR3, the 12 month safety study, adverse events were called to the investigators between study visits and reported at study visits, which occurred at study months 2, 4, 6, 9, and 12. In all three studies, subjects were allowed to use Bisacodyl as rescue medication if they had no bowel movement for four or more days or experienced severe discomfort. A complete medical history and physical exam (including a test for occult blood in the stool) was completed at enrollment for all three studies. A brief physical exam and second set of vital signs was completed at the final study visit. In studies 851-CR1 and 851-CR3, subjects provided blood and urine samples at enrollment and at the last study visit for a complete blood count, serum chemistries, and urinalysis. The study protocols allowed study investigators to reduce the dose of study drug in response to adverse events, but dose increases were not permitted.

The sponsor did not conduct label comprehension or actual use studies for this NDA, as they were not requested by FDA.

1.3.2 Efficacy

See the medical officer review from the Division of Gastrointestinal Products (DGP).

1.3.3 Safety

During three clinical studies, a total of 635 subjects were treated with MiraLax 17 g/day for one to 12 months. One hundred subjects were treated with matched placebo for up to six months. This population included 223 individuals of age 65 years and older and 99 *higher risk* individuals with underlying diabetes, renal disease and/or cardiac disease. Overall, these studies provide 301 patient years of use data to supplement the 200 years of patient use data that supported NDA 20-698 when MiraLax was approved for prescription marketing as a laxative to treat occasional constipation.

No deaths occurred during the drug development program. There were 39 serious adverse events, one of which may have been related to MiraLax use. A subject with sickle cell disease went into sickle crisis and was hospitalized for treatment. The crisis resolved. The laxative effect of MiraLax and the potential for associated minor changes in electrolytes and intravascular volume may have contributed to a relative state of dehydration in this individual over time, thereby making her more prone to sickle crisis.

Eighty-eight percent of MiraLax treated subjects completed the one month study; 62% of

MiraLax treated subjects completed the six month study (compared to 43% of placebo subjects); and 59% of subjects completed the 12 month study. The number of MiraLAX treated study drop-outs due to adverse events was as follows:

- One month study (851-ZCC): none
- Six month study (851-CR1): 19 (9%)
- Twelve month study (851-CR3): 23 (7%).

Ninety-five percent of these adverse events were gastrointestinal in nature. Among subjects ages 65 years and older, early discontinuation was less common than in the general study population.

Gastrointestinal (GI) adverse events overall were statistically more common in subjects treated with MiraLax compared to subjects treated with placebo. By individual GI adverse event (by preferred term) there were numerical, but not statistical, differences between treatment groups. The most common adverse events experienced by MiraLax treated subjects were: diarrhea (17%), loose stools (8%), flatulence (7%), and nausea (6%). Most GI adverse events were of mild to moderate intensity.

Adverse events associated with other body systems occurred with similar frequency in subjects treated with placebo and those treated with Miralax. Analysis of adverse event data by age, gender, race/ethnicity, and presence of concomitant higher risk medical conditions showed no statistically significant differences in adverse event rates between older/younger, male/female, Caucasian/non-Caucasian subgroups. These subanalyses did not reveal any significant differences between these subpopulations. The following numerical differences were noted by investigators:

- Caucasians experienced more GI adverse events than non-Caucasians (39% vs. 28%)
- Women had numerically more infections than men, mostly due to urinary tract infections.

Subjects 65 years of age and older did not experience an excess of adverse events compared to the study population as a whole, and as with the general study population, there were no significant differences in adverse event rates between Miralax and placebo treated groups other than for gastrointestinal adverse events. Subjects who experienced diarrhea did not have a higher incidence of other adverse events compared to subjects who did not experience diarrhea.

During the three clinical studies, Miralax dose was temporarily or permanently reduced in 53 subjects; 75% of these dose reductions were in response to events of diarrhea, loose stools, or increased flatulence. Data on the 184 study completers in study 851-CR3 were used to compare adverse event incidences in the first six months of MiraLax use compare to the second six months of MiraLax use. The adverse event incidences by body system were statistically the same except for GI and infection/infestation events which decreased in the second half of the study. The infection/infestation event rate was thought to be higher in the first half of the study due to the winter season.

High risk subjects (N = 99) from studies 851-CR1 and 851-CR3 experienced significantly higher rates of metabolism and nutrition disorder events, mostly due to preexisting hyperlipidemias. When data from high risk subjects from study 851-CR3 (N = 70) were considered alone, high risk subjects also had statistically higher incidences of infections and musculoskeletal disorders. Studies 851-CR1 and 851-CR3 included 42 individuals using narrow therapeutic index drugs. Five of these subjects required dose adjustments in their medication during study participation.

There were no clinically significant changes in mean laboratory values during the six and twelve month study periods for studies 851-CR1 and 851-CR3. All changes in mean laboratory values were small and within normal range. The sponsor noted statistically significant, but clinically insignificant, differences between groups for uric acid (all subjects), chloride (difference in baseline between elderly treatment groups), platelets (small decrease in both treatment groups), and cholesterol (small decrease in MiraLax subjects, small increase in placebo subjects).

The majority of subjects with abnormal laboratory results had abnormal laboratory assessments at baseline. Based on experimental laboratory ranges and a line listing of subjects with two or more consecutive abnormal laboratory values, this reviewer noted the following trends:

- The incidence of newly abnormal or increasingly abnormal laboratory values were similar for placebo and MiraLax treated subjects for: ALT, AST, bicarbonate, BUN, calcium, chloride, GGT, magnesium, potassium, and sodium.
- Creatinine increased from an already elevated baseline in 1% of placebo subjects and 2% of Miralax subjects in study 851-CR1.
- MiraLax treated subjects had a numerically greater incidence of high serum phosphate levels during study treatment.

There were no clinically significant changes in temperature of pulse. There were two MiraLax treated subjects with significant weight loss over the course of their respective studies. One of these individuals was an 81 year old female with multiple medical problems. She did not experience diarrhea. The second was a 29 year old female with no significant medical history including no history of an eating disorder. The highest blood pressure readings occurred almost exclusively in subjects with a history of hypertension. Nine of 304 subjects in study 851-CR1 had a normal BP reading at baseline and a high BP reading at the end of the study. All nine were in the MiraLax treatment group, but the placebo group had a higher number of subjects with hypertension at baseline.

Two subjects with a history of an eating disorder in the past were enrolled in the studies, complied with MiraLax dosing, and did not experience weight change during the studies. This reviewer was unable to find any published cases of MiraLax abuse by individuals with eating disorders, and the American Association of Poison Control Centers report submitted by the sponsor did not note cases of abuse in individuals with eating disorders. Cases of overdose that involved MiraLax without concomitant ingestion of other drugs

resulted in GI adverse events but no other clinically significant effects.

The sponsor provided data on 125 postmarketing adverse events reported with more than [redacted] units of MiraLax sold. Fifty-four of these events were classified as allergic reactions to PEG 3350, and 38 were gastrointestinal events. Nine of twenty-two 15-day report events involved off-label use in individuals under age 18 years, and eight were in children age 12 years or younger. While it is difficult to determine causality based on the limited information available, it is possible that the two seizure events (both pediatric) and three episodes of mouth sores were related to MiraLax use and likely that the episodes of diarrhea were related to Miralax use. The sponsor included an allergy alert in the draft label.

1.3.4 Dosing Regimen and Administration

The sponsor proposes approval of MiraLax for the treatment of occasional constipation in adults with a dose of 17 g/day [redacted]. Current directions for use instruct consumers to dissolve [redacted] MiraLax in four to eight ounces of beverage. Data previously submitted to the MiraLax prescription NDA (NDA 20-698) demonstrated product efficacy after seven to ten days of treatment. Currently available OTC laxatives marketed under the OTC Monograph limit duration of use to seven days. If MiraLax demonstrates efficacy after seven days of treatment in the studies submitted in support of this application, then the duration of use should be limited to seven days. In addition, the dose of MiraLax should be 17 g dissolved in eight ounces of beverage. This is consistent with the dosing and instructions provided in various clinical trials. The 17 g dose should preferably be packaged in single dose packets. If a larger container is considered, then the sponsor should provide a tool and directions that allow consumers to deliver a correct dose with each use.

1.3.5 Drug-Drug Interactions

No specific drug-drug interactions have been demonstrated with PEG 3350. The literature suggests that co-administration of MiraLax with digoxin results in a significant decrease in the Cmax and AUC of digoxin (Ragueneau et al, 1999). MiraLax's effect on GI absorption of drug may occur with other products as well. This is a common effect of laxatives and can be addressed through labeling language similar to that required on OTC laxative products marketed under the OTC monograph.

1.3.6 Special Populations

MiraLax was equally well tolerated by men, women, Caucasians, non-Caucasians, and

younger and elderly healthy individuals. Non-Caucasians tended to have fewer GI adverse events than Caucasians. Previously submitted studies suggest that elderly, debilitated individuals living in long term care facilities may experience higher incidences of diarrhea with the 17 g/day dose of MiraLax even with short term treatment.

Pregnant and breastfeeding women were excluded from all clinical studies of MiraLax. Reproductive toxicology studies in animals were negative according to the pharmacology/toxicology review by Dr. Tamal Chakraborti.

2. INTRODUCTION AND BACKGROUND

On December 6, 2005, Braintree Laboratories submitted NDA 22-015 for the nonprescription marketing of MiraLax OTC for the treatment of occasional constipation in adults. MiraLax was approved as a prescription-only treatment for occasional constipation on February 18, 1999, on the second review cycle for NDA 20-698.

2.1 Product Information

MiraLax (polyethylene glycol 3350, NF white powder for solution) is a synthetic polyglycol with an average molecular weight of 3350 that is not absorbed from the gastrointestinal tract. Chemically, polyethylene glycol 3350 (PEG 3350) is a water soluble, linear diol with a repeating oxyethylene unit and the following chemical formula:

$$HO(C_2H_4O)_{75}C_2H_4OH.$$

MiraLax (PEG 3350) is a white, free-flowing powder that readily dissolves in water to form a tasteless solution. The drug may also be dissolved in 8 oz. of another type of beverage. MiraLax is a pharmacologically inert, minimally absorbed, non-metabolized osmotic laxative that causes retention of water in the bowel lumen.

The applicant proposes the following conditions of use for MiraLax OTC:

- Target population: adults (lower age limit unspecified but clinical trial recruitment began at age 18 years)
- Indication: Relief of occasional constipation
- Dosing regimen [redacted] (17 g) or fill to top of white section in cap, completely dissolve in 4 to 8 oz. of beverage and drink - once daily
- Duration of use: [redacted] (although no duration of use is specified in proposed labeling).

The applicant states that with treatment for occasional constipation in adults, effective relief is generally attained after 1 – 3 days of use.

2.2 Currently Available Treatment for Indications

Symptoms of constipation are very common with a prevalence up to 20% depending on the data source. Most experts consider three stools per week the lower limit of normal stool frequency. The Rome consensus criteria for constipation include two or fewer bowel movements (BMs) per week in the presence of straining, hard stools, or a feeling of incomplete evacuation with at least 25% of BMs. Symptoms described by patients include: straining, stools that are excessively hard, unproductive urges, infrequency, and a feeling of incomplete emptying. Constipation is more common in women than men and increases with advancing age.[1] Functional constipation is a major feature of two colorectal motility disorders that may exist alone or in combination:

- Slow-transit constipation
  The primary defect is slower than normal movement of contents from the proximal to the distal colon and rectum. The slow transit may have a dietary or cultural basis in some individuals.

- Pelvic floor dysfunction
  The primary failure is inability to adequately evacuate the contents of the rectum even when the stool is soft. It is often accompanied by perineal descent and requires manual manipulation from the vagina, perineum, or rectum to clear the stool.[2]

The symptom of constipation may also arise secondary to another medical condition including:

- Primary diseases of the colon (stricture, cancer, anal fissure, proctitis)
- Metabolic disturbances (hypercalcemia, hypothyroidism, diabetes mellitus)
- Neurological disorders (Parkinsonism, spinal cord lesions).

For the initial evaluation and treatment of constipation symptoms, the American Gastroenterological Association (AGA), the American Academy of Family Practitioners (AAFP)[3] and sources from the National Institutes for Health (NIH)[4] all recommend an

[1] Constipation. Section I: General Approach to Gastrointestinal Diseases. Current Diagnosis and Treatment in Gastroenterology, 2nd edition. 2003.
[2] American Gastroenterological Association Medical Position Statement: Guidelines on Constipation. Gastroenterol. 2000; 119: 1761 – 78.
[3] Constipation: Keeping Your Bowels Moving Smoothly. AAFP. http://familydoctor.org/037.xml
[4] http://digestive.niddk.nih.gov/ddiseases/pubs/constipation/index.htm; http://www.nlm.nih.gov/medlineplus/ency/article/003125.htm

initial medical history and physical exam to rule out metabolic and structural problems and irritable bowel syndrome and to obtain baseline laboratory assessments. The vast majority of constipated patients have mild symptoms that are not associated with a structural abnormality, intestinal motility disturbance, or a systemic disease. These individuals have idiopathic functional constipation. Treatment should begin with increases in dietary fiber, through food and supplements, and an increase in fluid intake (at least 1.5 liters per day) and activity. If these interventions are not effective, then a laxative may be needed.

The Tentative Final Monograph (TFM) for Laxative Drug Products for OTC Human Use recognizes occasional constipation as a self-diagnosable condition and defines constipation and laxative as follows:

- Constipation: Infrequent or difficult bowel movements (BMs)

- Laxative: Any agent used for the relief of constipation.

The Advisory Panel for Laxative Drug Products recommended that constipation be defined as BM frequency less than three times per week but never specified other diagnostic criteria.[5]

Except for prescription-only MiraLax and generic PEG 3350 products approved under ANDAs, all other laxatives indicated for the relief of occasional constipation are regulated and marketed under the Over-the-Counter (OTC) Drug Monograph. The TFM for Laxative Drug Products was published on January 15, 1985, and has been amended several times. The Final Monograph is being written.

For laxative drug products, Category I active ingredients include:

- Bulk-forming laxative ingredients
  - Cellulose (semisynthetic)
  - Carboxymethylcellulose sodium
  - Methylcellulose
  - Polycarbophil
  - Polycarbophil sodium
  - Psyllium ingredients
  - Plantago seed
  - Psyllium husk
  - Psyllium hydrophilic mucilloid
  - Psyllium hemicellulose
  - Wheat bran

- Hyperosmotic laxative ingredients
  - Glycerin
  - Sorbitol

[5] Laxative Drug Products for Over-the-Counter Human Use - Advance Notice of Proposed Rulemaking (03/21/1975). 40FR1292

- Lubricant laxative ingredients
  - Mineral oil

- Saline laxative ingredients
  - Magnesium citrate oral solution
  - Magnesium hydroxide
  - Magnesium sulfate
  - Sodium phosphates oral solution
  - Sodium phosphates rectal solution

- Stimulant laxative ingredients
  - Bisacodyl
  - Castor oil
  - Dehydrocholic acid
  - Sennosides (from senna, senna fluid extract, senna oral solution, senna syrup USP)

- Stool softener laxative ingredients
  - Docusate calcium
  - Docusate potassium
  - Docusate sodium

- Carbon dioxide-releasing laxative ingredients
  - Combined monobasic sodium phosphate anhydrous, sodium acid pyrophosphate, and sodium bicarbonate
  - Combined sodium bicarbonate and potassium bitartrate

- Permitted combinations of laxative active ingredients
  - Plantago seed with any psyllium ingredient
  - Methylcellulose with any psyllium ingredient
  - Wheat bran with any psyllium ingredient
  - Sennosides with any psyllium ingredient
  - Mineral oil and magnesium hydroxide
  - Carboxymethylcellulose sodium and docusate sodium
  - Docusate sodium and glycerin
  - Docusate potassium and sorbitol

With the exception of sodium phosphates which will have a labeled duration of use of three days in the Final Monograph, labeling for all other laxative products instructs consumers to discontinue use and see a doctor if they need to use a laxative for more than seven days.

2.3 Availability of Proposed Active Ingredient in the United States

MiraLax and generic PEG 3350 drug products are indicated for the treatment of occasional

constipation. Otherwise, PEG 3350-containing drug products are prescription drugs intended for gastrointestinal lavage (bowel or colon cleansing) prior to colonoscopy or barium enema radiology exams. The first PEG product was marketed in the United States in 1984. Off label, these gastric lavage products are also used to cleanse the bowel prior to abdominal/pelvic surgeries where bowel surgery is planned or bowel injury is a substantial risk. When used for gastrointestinal lavage, the PEG 3350 is mixed with electrolytes. These products include:

- Colyte and GoLytely
  236 g PEG 3350 with 5.86 g sodium chloride, 2.97 g potassium chloride, 6.74 g sodium bicarbonate, and 22.74 g sodium sulfate). Use is indicated only in adults.

- NuLytely
  420 g PEG 3350 with 11.2 g sodium chloride, 1.48 g potassium chloride, and 5.72 g sodium bicarbonate. Use is indicated in adults and children as young as six months of age.

The powder is mixed with four liters of liquid and three to four liters are consumed over a three to four hour period to effect bowel cleansing.

Contraindications to use include: ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or toxic megacolon. The products should be used with caution in individuals with ulcerative colitis.

2.4 Important Issues With Pharmacologically Related Products

The Office of Drug Surveillance and Epidemiology completed a review of post-marketing adverse events (Adverse Event Reporting System data and literature) associated with PEG 3350 bowel cleansing from the time of product marketing through 2005 and identified the following serious adverse events:

- **4 fatalities**
  Three of the fatalities involved patients with underlying conditions including renal insufficiency, megacolon, and a history of bowel perforation which may have contributed to their events.

- **5 seizures, all with associated hyponatremia and one with associated death**
  One grand mal seizure event occurred in a 51 year old male with diabetes and end stage renal disease (ESRD) who then had fatal cardiopulmonary arrest. The PEG product labels state that administration of PEG results in virtually no net absorption or excretion of ions or water and that large volumes may be administered without significant changes in fluid or electrolyte balance; however, cases of clinically significant changes in electrolytes have been reported to AERS and in the medical literature, particularly in patients using diuretics or with underlying renal insufficiency.

- **1 case of cardiopulmonary arrest preceded by seizure and resulting in death (see above)**

- **1 case of acute renal failure**
  This case occurred in a 58 year old male one day after using one gallon of PEG. The patient had a history of end stage liver disease, ascites, and portal hypertension and was using furosemide and aldactone.

- **1 case of ventricular fibrillation**
  This event occurred in a 86 year old female with a serum potassium of 2.7 at the time of the event. She was successfully cardioverted.

This safety review also noted that there is some evidence from AERS reports that MiraLax and Glycolax, while indicated only for occasional constipation, are used clinically as bowel cleansers. The bowel cleansing dose for PEG 3350 (236g) is ingested over a three to four hour period of time. It is important to note that the recommended PEG 3350 dose for relief of occasional constipation is 17 g per day for up to 14 days. The amount of PEG consumed over two weeks for treatment of occasional constipation is the same as the amount consumed over four hours to achieve bowel cleansing.

2.5 Presubmission Regulatory Activity

Braintree Laboratories, Inc. conducted MiraLax drug development under IND 28,306 and subequently submitted NDA 20-698 on February 26, 1996. On February 18, 1999, MiraLax was approved on its second review cycle as a prescription drug for the treatment of occasional constipation in adults ages 18 years and older. Approval was based on data from two pivotal clinical trials, 851-3 and 851-6. Studies 851-4 and 851-5 provided supportive data. Data from Study 851-3 showed that a majority (73%) of subjects had at least one BM by the second day of therapy. **The medical reviewer stated that the findings appeared to justify the protocol specified 10-day treatment period.** Of 161 subjects overall who received 17 g/day MiraLax, 24 were age 65 years old or older. Of these, three experienced diarrhea (two from Study 851-5; one from Study 851-5). There were no statistically significant differences between the age of subjects who experienced diarrhea and those who did not while using 17 g/day of MiraLax. The sponsor also submitted data from an open-label study (851-4a) of 136 patients who were enrolled for ad-lib treatment with MiraLax for an unlimited period of time. Sixteen patients used the product for five years or longer. Older nursing home residents tended to use a reduced dose (12-13 g), and this dose was well tolerated. **The medical team leader recommended approval of MiraLax for the treatment of occasional constipation based on the results of Study 851-6 supported by the results of Study 851-3.** Labeling issues included dose adjustment in the elderly (based on results from Study 851-4) and the delayed onset of action of 48 – 96 hours. The resubmission included a protocol for a Phase IV trial, an open-label, multicenter trial in adults designed to address the question about the therapeutic

course of constipated patients following a 14-day course of therapy with MiraLax 17 g/day. The action letter noted the Phase IV commitments specified in the submission. All post-marketing commitments were later fulfilled (04/23/04) but this reviewer was unable to locate a review of the submitted postmarketing study or the study report submitted by the sponsor.

[redacted]

On September 6, 2000, Braintree met with DGP and the Division of Over-the-Counter Drug Products (now the Office on Nonprescription Products, ONP) to discuss a proposed prescription-to-OTC switch for MiraLax. FDA expressed some reservations about the plan including concerns about indiscriminate use in the elderly, renally impaired, pregnant, and eating disorder populations. [redacted] At that time, FDA told the sponsor that an actual use study would be needed and that a label comprehension study was probably not needed for approval but should be used to develop a well-comprehended label for the actual use study.

[redacted]

[redacted]

DGP completed Special Protocol Assessments (SPAs) for Protocols 851-CR1, 851-CR2[6], and 851-CR3 which were designed as clinical trials to support the [redacted] use indication for MiraLax and the proposed OTC switch. Based on protocol review, FDA informed the applicant that the data obtained from the three studies should provide adequate long term safety data; however, data adequacy would be a review issue.

[redacted]

Reviewer comment:

[redacted]

The clinical review team also included the following study protocol recommendations:

- The primary efficacy endpoint should be three or more BMs per week and the absence of any other Rome criteria (as stated in the protocol)
- Provide a rescue medication and specify conditions for use in patients with constipation unrelieved by MiraLax
- Ensure that patients have had a workup for reversible causes of chronic constipation prior to study entry
- Women of childbearing age who enroll in the study should be using birth control
- Enroll a population of individuals who fit the [redacted] constipation. Entry criteria should be 12 weeks with stool less frequent than three per week along with three months of at least one of the other Rome criteria.
- Perform serum TSH at screening and exclude individuals with hypo- or hyperthyroidism
- Develop a list of prohibited concomitant medications that can affect or effect bowel movements and exclude patients expected to use these medications for a prolonged period of time
- Enroll a sufficient number of geriatric patients to assess efficacy and safety in this subpopulation.
- Do not replace subjects who drop out of the study

[6] It is not clear if Protocol 851-CR2 later became Study 851-ZCC which is reviewed in this application along with Studies 851-CR1 And 851-CR3.
[7] Constipation. Section I: General Approach to Gastrointestinal Diseases. Current Diagnosis and Treatment in Gastroenterology, 2nd edition. 2003.

- Exclude patients who do not utilize the Interactive Voice Response System (IVRS) a minimum of 12 days during the 14 day observation period
- Specify how missing data from the IVRS during the study period will be handled in analysis

A follow-up meeting on July 9, 2003, defined treatment success for Protocol 851-CR1. Based on ongoing debate over which endpoint was most [redacted] constipation indication, FDA stated that the application would go before an Advisory Committee.

Braintree and FDA met most recently on May 2, 2005, for a pre-NDA meeting for a proposed Rx-to-OTC switch of MiraLax for the treatment of occasional constipation in adults [redacted] with a [redacted] duration of use. The applicant intended to submit complete reports on studies 851-CR1, 851-CR3, and 851-ZCC to support the application for the adult population and study 851-15 [redacted] Although a written request for pediatric studies was issued by DGP [redacted]

[redacted] FDA agreed that the completed clinical studies (851-CR1, 851-CR3, 851-ZCC) appeared adequate to support a MiraLax OTC NDA for the adult population. FDA reminded the applicant to include appropriate data-driven recommendations for dose adjustment in patients with renal impairment and stated that an actual use study was not needed.

Reviewer comments:

[redacted]

sodium phosphates solution.

Following the July 2005 meeting, FDA informed Braintree that the MiraLax OTC label should read: *Stop use and ask a doctor if you need to use a laxative for longer than one week.* The applicant expressed their disagreement with this statement in an October 28, 2005, letter from [redacted] for Braintree Laboratories, Inc. The counselor noted that the Rx-to-OTC MAPP 6020.5 specifically states:

> *It is **NOT** necessary for OTC drug products marketed under the authority of an approved NDA to conform to wording/labeling in OTC drug monographs for similar products. Nonetheless, every effort should be made to keep labeling for NDA products as similar as possible to similar monographed OTC drug products.*

[redacted] cited NDA approvals for OTC marketing of Prilosec OTC®, Abreva®, and Lotrimin Ultra® to support his argument that an OTC laxative approved under a NDA could be considered for a 14 day course of therapy.

2.6 Other Relevant Background Information

The applicant did not submit any information on international marketing. However, this reviewer performed a PubMed search using the terms PEG 3350 and constipation and found evidence of international use. There are published articles reporting treatment of constipation in the United Kingdom and the Netherlands with PEG 3350, either with or without electrolytes, in children and adults.[8] There is a PEG 3350 monograph in the European Pharmacopoeia but not in the British Pharmacopoeia.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

[8] Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJ, Grootenhuis MA, Derkx BH, Benninga MA. Health related quality of life in disorders of defecation: the Defecation Disorder List. Arch Dis Child. 2004 Dec; 89(12):1124-7.

See the CMC review by Shulin Ding of the Office of New Drug Quality Assessment (ONDQA).

3.2 Animal Pharmacology/Toxicology

The pharmacology review by Tamal K. Chakraborti, Ph.D., states that nonclinical studies conducted with MiraLax PEG 3350 adequately support its use at the intended therapeutic dose and in accordance with product labeling.

The systemic toxicity of PEG 3350 was adequately evaluated in a complete range of acute, subacute/subchronic, and chronic toxicity studies in mice, rats, and dogs. These studies include chronic oral toxicity studies in rodents and non-rodents and an adequate battery of genotoxic tests. Studies in mice and rats evaluated the carcinogenic potential of PEG 3350. Reproductive and fertility studies for PEG 3350 were completed in rats; teratology studies were completed in rats and rabbits and evaluation of peri- and post-natal development was done in rats.

Study results suggest that the target organs of toxicity vary across species. MiraLax PEG 3350 toxicology studies showed the following changes:

- Rat: focal or multifocal cytoplasmic vacuolation in cortical tubular epithelium in males at 6 g/kg/day.
- Dog:

  After oral administration for 28 days,
  - Lungs: minimal to moderate interstitial fibrosis with thickening of alveolar septa and pneumocyte hypertrophy and hyperplasia
  - Gastrointestinal (GI) tract: minimal subacute inflammation or crypt abscesses, hemorrhage, and lymphoid hyperplasia in the cecum, colon, ileum and/or rectum in female animals at 3, 6, and 9.3 g/kg/day.
  - Testes: hypospermia in the epididymides, seminiferous tubule degeneration and multinucleated spermatids.
  - Salivary gland atrophy.

  After oral administration for nine months:
  - Testes: retarded development
  - Prostate: lymphocyte infiltrate
  - Mammary gland hyperplasia (females)
  - Liver vacuolation (females)
  - Gallbladder: lymphocytic infiltrate and epithelial hyperplasia (females)

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.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of data for this clinical safety review include the following:

Materials submitted in support of NDA 22-015

- Three clinical trials:
  - Study 851-CR1: Extended use of MiraLax in constipated patients
  - Study 851-ZCC: MiraLax vs. Zelnorm in treatment of patients with chronic constipation
  - Study 851-CR3: An open label study of chronic MiraLax use in constipated patients.

- Five human pharmacokinetic (PK) studies
  - Single dose PK evaluation of MiraLax in normal volunteers
  - Multiple dose PK study of MiraLax
  - Open-label, multiple-dose study to assess the effect of age on the plasma and urine PK of MiraLax in healthy adult subjects
  - Effect of renal disease on the multiple dose PK of MiraLax

- Postmarketing data up to August 2005
- Literature
  The applicant submitted 32 articles. Seven contain useful safety data.

Additional materials reviewed:
- Published literature on the use of PEG 3350 for the treatment of constipation (PubMed search terms: PEG 3350 and constipation)

4.2 Tables of Clinical Studies

Table 1 is a tabular listing of all clinical studies that provided safety data for this review.

Table 1: Clinical Studies Supporting NDA 22-015		
Study	**Type of Study**	**Comment**
Pharmacokinetic studies		
851-PK-001	Single dose PK	Healthy volunteers
851-PK-002	Multiple dose PK	14 healthy adult volunteers received 17 g/day MiraLax for 7 days.
851-PK-004	Multiple dose PK	6 healthy adult volunteers and 6 patients with End Stage Renal Disease (ESRD) received 17 g/day MiraLax for 7 days.
851-PK-005	Open-label, multiple dose PK, healthy volunteers	Assess effect of age on plasma and urine PK of PEG 3350 - 24 healthy adult volunteers received 17 g/day MiraLax for 7 days.
851-PK-006	Open-label, multiple dose PK, patients with renal disease	Assess PK profile of MiraLax in patients with ESRD. Blood samples from this study were also used to evaluate the hemodialyzability of PEG 3350 in-vitro
Clinical efficacy and/or safety studies		
851-CR1	Double blind, placebo-control, randomized trial in patients with chronic constipation	180 day study preceded by 14 day placebo run-in. 302 subjects randomized 2:1 to MiraLax 17 g/day or matched placebo. Dose reductions allowed for adverse events.
851-ZCC	Double blind, active comparator, randomized trial in patients with chronic constipation	28 day study 237 subjects randomized 1:1 to treatment with MiraLax 17 g/day or Zelnorm 6 mg bid.
851-CR3	12 month, open-label, multicenter trial in patients with chronic constipation	Twelve month study. 311 adult subjects ages 18 years and older treated with MiraLax 17 g/day. Dose reductions allowed for adverse events.

4.3 Review Strategy

This review covers safety data submitted to support NDA 22-015 as outlined above. Safety data previously reviewed for approval of NDA 20-698 has been requested from the sponsor. The clinical review from DGP reviews the efficacy data submitted in support of this application. The review by Reynold Tan, Ph.D., interdisciplinary scientist from the Division of Nonprescription Regulation Development, reviews the proposed product labeling.

This safety review presents safety data on patients using MiraLax who have chronic constipation as the studies submitted in support of the NDA were conducted in this population. These data will be compared to the adverse event profiles of subjects from the short term studies submitted to NDA 20-698. The review looks at the clinical safety data for correlations and relationships between adverse event incidences with short term and long term product use and for further support in additional published literature.

4.4 Data Quality and Integrity

DSI reported four study site inspections related to NDA 22-015: two sites from Study 851-CR1 and two sites from Study 851-ZCC. At all four sites, the inspectors audited the records for all randomized subjects. Data generation was acceptable at all four sites and three sites demonstrated adequate study conduct. DSI found that one study site for 851-CR1 did not maintain adequate records of drug disposition, including dates, quantities, and use by subjects and requested voluntary corrective actions. The inspector noted three minor deviations at a 851-ZCC site but no corrective actions were needed. Detailed information on these DSI reports is available in DFS.

4.5 Compliance with Good Clinical Practices

The clinical and pharmacokinetic studies were conducted according to ICH/GCP guidelines and HIPPA Privacy Regulations including archiving of essential documents. Periodic visits were conducted by [redacted] (an auditing company) at all participating study sites to ensure compliance with the protocol and GCPs. Portions of the studies were audited and checked for compliance with applicable Federal Regulations [redacted]. Independent quality control audits were performed by Braintree personnel.

The investigators were responsible for explaining the purpose, nature, and potential risks of the study to each subject and guardian. Study staff obtained patient informed consent for all study participants in accordance with 21 CFR parts 50 and 56. Patient consent was obtained at prescreening, prior to baseline evaluation and study enrollement. Clinical site staff maintained an on-site file of informed consent forms.

4.6 Financial Disclosures

The applicant has enclosed the Financial Interests and Arrangements of Clinical Investigators Certifications. These documents raise no questions regarding integrity of the study data.

5. CLINICAL PHARMACOLOGY

MiraLax is a synthetic polyglycol with an average molecular weight of 3350 (PEG 3350). The actual molecular weight is not less than 90.0% and not greater than 110.0% of the nominal value. The chemical formula is:

$$HO(C_2H_4O)_nH \quad (n = 68 - 84).$$

At less than 55 degrees Celcius, PEG 3350 is a free flowing white powder that is freely soluble in water.[9]

5.1 Pharmacokinetics

PEG is a pharmacologically inert osmotic agent that causes water retention in the stool. In the past, PEG 3350 could be detected in urine and feces but not in serum. To support the PK studies performed for this application, Braintree developed and validated a specific and sensitive assay for PEG 3350 using High Performance Liquid Chromatography – Tandem Mass Spectroscopy which can detect PEG serum levels down to [redacted] and urine levels as low as [redacted]. This test is [redacted] more sensitive than techniques previously used to detect PEG in urine and serum.

Following a 17 g oral dose, PEG 3350 was detectable in plasma as early as 30 minutes and reached a C_{max} of 353 – 1111 ng/mL in a mean T_{max} range of 2.0 – 5.4 hours. In most subjects, PEG 3350 was undetectable in serum between 18 and 24 hours post-dose. Serum half-life ranged between 3.6 – 8.0 hours in healthy young and elderly adults. PEG 3350 was detectable in urine for up to 60 hours post-dose. Following multi-dose administration in individuals with normal or mildly impaired renal function, the AUC did not increase significantly, without any detectable accumulation of PEG 3350 over time. PEG 3350 was not detectable in serum prior to repeat dosing. In patients with end stage renal disease (ESRD), defined as a creatinine clearance of less than 15 mL/minute, C_{max} and AUC exceeded those in normal volunteers by factors of 2.3 and 5 respectively. Half-life of PEG 3350 was prolonged by a factor of nine. PEG 3350 was detectable in serum before repeated doses and at 24 – 48 hours post-dose. The mean serum levels 24 – 48 hours post-dose exceeded the C_{max} observed in most normal volunteers. Braintree completed an in-vitro study demonstrating that PEG 3350 can be removed from the serum using hemodialysis.

The systemic exposure to PEG 3350 in humans, regardless of age, is low, and the small amount absorbed is rapidly cleared from the plasma. The primary excretion route for absorbed PEG appears to be renal. Based on PEG recovery from the urine, about 0.15 – 0.30% of the 17 g daily dose is absorbed. Fecal recovery of PEG 3350 was nearly 100% from the majority of subjects dosed with 17 g per day of MiraLax. For the entire study population, fecal recovery of PEG 3350 was 93%. About 38% of a PEG dose is recovered in the feces in the first 24 hours post-dose. Most of the fecal excretion of PEG occurs 24 – 96 hours after dosing, when serum PEG is already undetectable. Mean PEG excreted per day increases from Day 1 – Day 4 post-dose as mean daily fecal weight increases.

[9] Mosby' Drug Consult, 16th edition, 2006. http://online.statref.com

There were no consistent gender or racial differences in pharmacokinetic (PK) parameters and no statistically significant differences in key parameters between adults ages 18 – 40 years and elderly adults with mildly impaired renal function.

In-vivo studies have not shown any effect of PEG on the active absorption or secretion of glucose or electrolytes in the bowel. PEG is not a substrate for colonic bacterial growth – in vitro studies show that incubation of PEG 3350 with human feces does not increase the amount of hydrogen and methane formed compared to control incubates. In human studies, there is no evidence of tachyphylaxis.[10]

There are no reported PK drug-drug interactions for PEG 3350. In a study by Padoin et al (1995), PEG 3350 did not alter the PK of amoxicillin.[11]

5.2 Pharmacodynamics

PEG 3350's pharmacodynamic action in the bowel leads to retention of water in the stool. While a PEG 600 solution shows a negligible difference between predicted and observed osmolarity at all concentrations, a PEG 3350 solution exerts a greater osmotic effect than that predicted based on the number of molecules in solution. This effect increases with increasing PEG solution concentration. This effect may be due to water sequestering where the very long molecules of PEG 3350 (with 68 – 84 glycol units) order a large region of water. Through this pharmacodynamic mechanism, PEG 3350 increases water in the colon resulting in increased stool mass, hydration, volume, and lubrication. Data on gastric motility and oral-anal transit times are not consistent.

PEG 3350 gastric lavage drug products are formulated with electrolytes to prevent net gain or loss of electrolytes from any resulting diarrhea, so similarly, early drug development studies evaluating the laxative effect of PEG 3350 looked at formulations containing electrolytes. Analysis of the electrolyte content of the subjects' stools following treatment revealed that all electrolytes included in the laxative formulation were completely absorbed. This occurred at doses up to 252 g when administered in divided daily doses. For this reason, the MiraLax formulation contains only PEG 3350.

A few published articles document pharmacodynamic (PD) effects of orally administered PEG 400 (used as an excipient in drugs) on griseofulvin (Hansford et al, 1980)[12] and

[10] Mosby' Drug Consult, 16th edition, 2006. http://online.statref.com

[11] Padoin C, Tod M, Brion N, Louchahi K, Le Gros V, Petitjean O. Pharmacokinetics of amoxicillin coadministered with a saline-polyethylene glycol solution in healthy volunteers. Biopharm Drug Dispos. 1995; 16(3): 169 – 76.

[12] Hansford DT, Newton JM, Wilson CG. The influence of formulation on the absorption of orally administered griseofulvin preparation in rabbits. Pharm Ind. 1980; 42: 646 – 50.

ranitidine (Basit et al, 2002).[13] However, there are no documented PD drug-drug interactions with PEG 3350.

5.3 Exposure-Response Relationships

During the drug development process for MiraLax, Braintree performed dose ranging studies evaluating doses of 6 – 52 grams of PEG 3350. Diarrhea tended to occur with the 52 g dose and was more common at the 34 g dose than at the 17 g dose.

Braintree Study 851-3 was a pivotal safety and efficacy study submitted in support of NDA 20-698. It included treatment arms with 17 g per day and 34 g per day of MiraLax for 10 days. Results showed a statistically significant dose dependent increase in BM frequency and stool output. At the 34 g dose, some patients reported diarrhea or loose stools.

Study 851-4 was conducted in elderly nursing home residents. The study was identical to Study 851-3 and subjects were randomized to 17 g or 34 g per day of MiraLax for 10 days to treat occasional constipation. The first five subjects experienced diarrhea, so the doses were reduced to 6 g and 12 g for the remaining study subjects. A dose response was not demonstrated in this study, but there were statistically significant differences in BM frequency and stool output between the placebo control period and the first treatment period. (See 06/02/98 NDA 20-698 Medical Officer Review by Hugo Gallo-Torres, MD Ph.D., clinical team leader, DGP).

6. INTEGRATED REVIEW OF EFFICACY

Please see the medical officer review from the Division of Gastrointestinal Products, for the integrated review of efficacy.

[13] Basit AW, Podczeck F, Newton JM, Waddington WA, Ell PJ, Lacey LF. Influence of polyethylene glycol 400 on the gastrointestinal absorption of ranitidine. Pharm Res. 2002; 19(9): 1368 – 74.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

As previously shown in tabular form in Section 4.2, the applicant submitted safety data to support this NDA from a variety of sources:

- Clinical trials
  - 851-CR1: Randomized, double-blind, placebo-controlled, multicenter six-month safety and efficacy trial
  - 851-CR3: Open-label, multicenter 12-month safety trial
  - 851-ZCC: Open-label, randomized, active comparator one month safety and efficacy trial

- Pharmacokinetic studies
- Post-marketing safety data
- Literature review.

Safety data from the three clinical trials will be presented together. While study 851-CR1 was the only double-blind, placebo-controlled trial, the use of the same inclusion and exclusion criteria and nearly identical definitions for constipation allow some comparisons across studies among the MiraLax treatment groups as compared to the placebo group. Where data is combined for the Miralax treatment groups from studies 851-CR1 and 851-CR3, the data is presented separately as well as combined. The pharmacokinetic studies are reviewed in detail by Tien Mien Chen, reviewer from the Office of Clinical Pharmacology. The adverse event data from these PK studies will be presented in this review.

Appendix 10.1 contains detailed summaries of Studies 851-CR1, 851-CR3, and 851-ZCC. These study designs and methods are summarized below.

For all three clinical trials, inclusion criteria included the following definition of constipation based on modified ROME criteria:

- Less than three satisfactory stools per week
- One or more additional ROME based criterion in more than 25% of defecations (straining, lumpy or hard stools, or sensation of incomplete evacuation).

Screened individuals were excluded for :

- Heme positive stool at screening

- Hypo- or Hyperthyroidism (by history or TSH)
- Suspected perforation/obstruction
- History of gastric retention, inflammatory bowel disease (IBD), bowel resection, or colostomy
- Known organic cause for constipation
- Loose stools and sufficient criteria for irritable bowel syndrome (IBS)
- Using medication that affects bowel habits: anti-diarrheals, antacids, anticholinergics, antispasmodics macrolides, 5-HT_3 and 5-HT_4 receptor antagonists, narcotics, prokinetics, selective serotonin reuptake inhibitors or tricyclic antidepressants (if not on a stable dose for at least one month), calcium antagonists (unless on a stable dose for at least one month)
- Breastfeeding, pregnancy, intent to become pregnant, lack of reliable contraception throughout the study in women of childbearing potential.
- Known allergy to PEG and/or corn and/or Zelnorm ingredients (depending on the study).

For subjects treated with MiraLax or MiraLax placebo, the timing of the daily dose was not specified. In addition to study drug, subjects in all three studies received bisacodyl 5 mg tablets to use as rescue medication. The rescue medication instructions were to take bisacodyl 10 mg for severe discomfort or for lack of a BM in four days.

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

In this Phase III, randomized, double-blind, parallel, placebo-controlled, multi-center study, normal, constipated outpatients were randomized 2:1 to treatment with 17g per day of MiraLax (N = 204) or placebo (N = 100) for six months.

Eligible subjects had a 14 day screening period during which they were prohibited from using laxatives and gained experience in reporting daily BM habits via the interactive voice response system (IVRS). In order to proceed to randomization, patients needed to meet the study definition of constipation as defined above and could not miss more than one day of IVRS reporting during the screening period. Subjects who missed IVRS reporting on Day 14 were not eligible for randomization.

Six hundred nine eligible subjects entered the 14 day screening period. After the 14 day period, 304 subjects were enrolled. One hundred fifteen subjects did not meet the BM criteria during the screening period; 73 subjects no longer met study inclusion/exclusion criteria; 74 were withdrawn by the investigator for non-compliance with the study protocol, and 40 subjects withdrew consent. One subject experienced an adverse event. The sponsor did not provide information on subjects who failed to meet inclusion and exclusion criteria at the initial screening visit and did not provide specific reasons for not meeting these criteria following the 14 day screening period.

Following the screening period, eligible subjects were randomized to one of the two treatment arms. Study drug was packaged in individual daily doses. During the study,

subjects used the IVRS to provide daily reports on bowel habits and adverse events. At monthly study center visits, subjects brought any unused study drug and rescue medication for investigator review and received additional study drug and rescue medication as needed. In addition, the investigators collected blood and urine samples for hematology, serum chemistry, and urinalysis.

Of 609 individuals screened, 188 failed the study criteria, 40 withdrew consent, 74 were noncompliant with the study protocol, and one discontinued due to an adverse event. Of the 306 subjects enrolled in the study, one was randomized in error and one was noncompliant with the study protocol, leaving 304 men and women ages 18 years and older in the intent-to-treat population. The safety population included all subjects who took at least one dose of study medication and this included 100 subjects using placebo and 204 using MiraLax.

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

In this Phase IV open-label, multi-center study, subjects were normal, constipated 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.

Three hundred thirty-five subjects enrolled in the study. Twenty-four did not meet study inclusion and exclusion criteria. Three had heme positive stool and 21 had an abnormal TSH result. The intent-to-treat population included 311 subjects.

All subjects received a 527 g bottle of MiraLax and were instructed to use one capful (approximately 17 g) mixed in eight ounces of a beverage once daily. Study personnel instructed subjects to return to the study center for follow-up visits at 2, 4, 6, 9, and 12 months following enrollment. At these visits, subjects reported adverse events and provided blood and urine samples. Study personnel measured vital signs, reviewed unused study and rescue medication, and dispensed additional medication as needed.

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

In this Phase IV, randomized, open-label, parallel arm, multi-center study, normal constipated patients were randomized to treatment with either 17g of MiraLax per day or 6 mg Zelnorm bid for 28 days.

Two hundred thirty-seven subjects enrolled and received treatment. There were no subjects who failed to meet study criteria.

Following randomization, study personnel dispensed study drug and rescue medication to

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 system to report their daily BM experiences. The IVRS questionnaire was the same one used for Study 851-CR1 (see Section 10.1). This study initially enrolled men and women over age 18 years; however, enrollment of men and women over age 65 years was stopped in response to recommendations made at the July 14, 2004 FDA advisory committee meeting on treatment of irritable bowel syndrome with Zelnorm.

7.1.1 Deaths

There were no deaths in the PK studies or the three pivotal safety and efficacy trials. There were no deaths in trials 851-3, 851-4, 851-5, and 851-6 submitted to NDA 20-698 to support approval for prescription marketing of MiraLax.

7.1.2 Other Serious Adverse Events

Subjects from all submitted clinical studies reported a total of 39 serious adverse events. One event occurred in a patient with end stage renal disease (ESRD) in Study 851-PK-004/006. No SAEs occurred among subjects in Study 851-ZCC. Nine subjects experienced 12 SAEs during Study 851-CR1, which were evenly divided between the MiraLax and placebo treatment groups, and 18 subjects experienced 26 SAEs during the 12 months of Study 851-CR3. The sponsor did not consider any of the SAEs related to MiraLax treatment. Table 2 summarizes the SAEs by body system. In the appendices, under Other Pertinent Information, section 10.3 contains a detailed table describing each SAE.

Table 2: Number of Serious Adverse Events by MedDRA Body System: Studies 851-CR1, 851-CR3, 851-ZCC

Body System	MiraLax (N = 635)	Placebo (N = 100)
Blood and lymphatic system	1	
Cardiac	1	
Congenital, familial, genetic	1	
Gastrointestinal	3	
General and administration	1	
Infections and infestations	2	1
Injury, poisoning, and procedural	6	
Investigations	1	
Metabolism and nutrition	1	
Musculoskeletal, connective tissue	4	

Table 2: Number of Serious Adverse Events by MedDRA Body System: Studies 851-CR1, 851-CR3, 851-ZCC		
Body System	**MiraLax (N = 635)**	**Placebo (N = 100)**
Neoplasms benign, malignant	2	3
Nervous system	3	
Pregnancy, puerperium, perinatal	1	
Psychiatric	0	1
Renal and urinary	0	1
Respiratory, thoracic, mediastinal	2	
Surgery and medical procedures	2	
Vascular	1	
Total	32	6

The investigators concluded that all 39 SAEs were unrelated to study drug.

Reviewer comment:

1. *This reviewer agrees with the sponsor's assessment that the SAEs described appear unrelated to MiraLax use except possibly for the subject who developed sickle crisis.*

   The subject who developed sickle crisis did not experience diarrhea and had normal urine specific gravities before and after the event. However, individuals with sickle cell disease have an inability to concentrate urine, so their urine specific gravity never rises. The inability to concentrate urine may make individuals with sickle cell disease more sensitive to effects of laxatives as they may already be relatively volume depleted. The MiraLax induced laxative effect over time may have contributed to crisis precipitation.

7.1.3 Dropouts and Other Significant Adverse Events

In the three clinical studies submitted in support of NDA 22-015, subject discontinuation rates varied with the length of the study. In the one-month study (851-ZCC), 88% of MiraLax-treated subjects and 83% of Zelnorm treated subjects completed the study. In the 6 month study (851-CR1), 62% of MiraLax-treated subjects completed the study but only 43% of placebo-treated subjects completed the study. All subjects in the 12 month study (851-CR3) were treated with MiraLax, and 59% completed the study.

7.1.3.1 Overall profile of dropouts

The reasons for subject discontinuations in all three clinical studies are illustrated below in Table 3. Discontinuation rates were higher among subjects randomized to placebo than subjects using active treatment in any of the clinical trials, including the 12 month trial. For the one month trial (851-ZCC), none of the 120 subjects randomized to MiraLax discontinued early due to an adverse event. However, in the sixth month and 12 month studies, 9% and 7% of the subjects respectively discontinued early due to an adverse event. Three to five percent of study subjects lost to follow-up in the one month and six month studies, but 13% were lost to follow-up in the 12 month study. One to 12% of subjects using MiraLax discontinued early due to lack of efficacy compared to 26% in the placebo group in Study 851-CR1. Discontinuations due to noncompliance with protocol varied from 3 – 7% across studies and treatment arms.

Table 3: Reasons for Subject Study Discontinuation (Drop-outs)

Subject Disposition	851-CR1 (6 months)		851-CR3 (12 months)	851-ZCC (1 month)	
	Placebo N (%)	MiraLax N (%)	MiraLax N (%)	MiraLax N (%)	Zelnorm N (%)
Enrolled	100	204	311	120	117
Completing	43 (43%)	77 (62%)	184 (59%)	106 (88%)	97 (83%)
Discontinued	57 (57%)	77 (38%)	127 (41%)	14 (12%)	20 (17%)
Reasons:					
Withdrew consent	14 (14%)	14 (7%)	35 (11%)	6 (5%)	7 (6%)
Lack of efficacy	26 (26%)	24 (12%)	13 (4%)	1 (1%)	1 (1%)
Non-compliance	7 (7%)	9 (4%)	16 (5%)	4 (3%)	4 (3%)
Lost to follow-up	3 (3%)	11 (5%)	40 (13%)	3 (3%)	3 (3%)
Adverse event	7 (4%)	19 (9%)	23 (7%)	0	5 (4%)

As shown in Table 4 below, study subjects ages 65 years and older on active treatment with MiraLax or Zelnorm had lower rates of study discontinuation than the study population as a

whole. Elderly subjects randomized to placebo discontinued early at about the same rate as the general study population.

Table 4: Comparison of rates of subject discontinuation between study population ≥ 65 years of age and the total study population

Population	851-CR1		851-CR3	851-ZCC	
	Placebo	MiraLax	MiraLax	MiraLax	Zelnorm
Subjects ≥ 65 years of age					
Enrolled	24	51	117	17	14
Discontinued	13 (54%)	17 (33%)	35 (30%)	2 (12%)	1 (7%)
All study subjects					
Enrolled	100	204	311	120	117
Discontinued	57 (57%)	77 (38%)	127 (41%)	14 (12%)	20 (17%)

7.1.3.2 Adverse events associated with dropouts

Among the three clinical studies conducted to support NDA 22-015, forty-two of 635 subjects treated with MiraLax dropped out of their respective studies early due to an adverse event. These subjects ranged in aged from 19 – 86 years.

Among 204 subjects on MiraLax in Study 851-CR1, 20 (10%) withdrew from the study due to adverse events. Ninety-five percent of these adverse events were GI in nature and included: flatulence (25%), abdominal distension (15%), loose stools (15%), nausea (15%), and diarrhea (10%). By comparison, 7% of the 100 subjects on placebo discontinued the study early due to adverse events, and 71% of these events were GI in nature. These GI AEs were somewhat different from those seen among MiraLax users who discontinued and included: abdominal pain (29%), diarrhea (14%), dyspepsia (14%), and nausea (14%).

Reviewer comment:

Most of these differences can be explained by the fact that the placebo group was more constipated than the MiraLax group; however it is interesting to note that the placebo-treated individuals had a relatively higher incidence of diarrhea. Some of these subjects may have experienced leaking of watery stool around a plug of hard stool.

Table 5 lists all subjects, by study and study drug, who discontinued from the study due to an adverse event.

Table 5: Subject discontinuations due to adverse events in Studies 851-CR1, 851-ZCC, and 851-CR3

Subject	Demographics	Study Days	Adverse Event	Severity	Outcome
Study 851-CR1 (MiraLax)					
101-10	M, 22 yo, Cauc.	32	Elevated CPK	Mild	Unresolved
102-1	F, 46 yo, Cauc.	56 – 60	Increased gas, Intermittent watery stool	Mild	Resolved
104-5	M, 82 yo, Cauc.	18 – 55	Diarrhea	Moderate	Resolved
110-14	F, 44 yo, AA	54 – 83	Gastritis	Moderate	Resolved
112-24	F, 49 yo, AA	9 – 16	Intermittent loose stool	Mild	Unresolved
114-17	F, 48 yo, Cauc.	1 – 13	Fecal incontinence	Mild	Resolved
117-2	F, 41 yo, Cauc.	2 – 20	Nausea	Moderate	Resolved
119-6	F, 48 yo, Cauc.	119	Anemia	Mild	Unresolved (also with elevated LFTs – resolved)
119-7	F, 87 yo, Cauc.	1 – 3	Nausea	Moderate	Resolved
120-6	F, 39 yo, AA	9 - 12	Nausea	Mild	Resolved
121-18	F, 45 yo, Hispanic	2 – 6	Excessive abdominal bloating and gas	Severe	Resolved
122-10	M, 67 yo, AA	93	Prostate cancer	Severe	Unresolved
124-2	F, 69 yo, Cauc.	16 – 26	Intermittent diarrhea on reduced drug dose	Severe	Resolved
127-6	F, 46 yo, Cauc.	40 – 41	Bloating and excessive stool frequency	Moderate	Resolved
129-13	F, 63 yo, AA	≈ 32	Gas and fecal urgency with reduced drug dose for previous diarrhea	Moderate	Gas unresolved
131-6	F, 65 yo, Cauc.	24 – 45	Gas and loose stools	Moderate to severe	Resolved
132-1	M, 75 yo, Cauc.	≈ 96 - 126	Gas	Moderate	Unresolved
136-10	F, 54 yo, Cauc.	81 - 82	Fractured ankle Head laceration	Severe Moderate	Resolved with sequelae
141-14	F, 67 yo, Cauc.	≈ 80	Cellulitis of left elbow, confusion, fatique	Mild to Moderate	Unresolved
149-19	F, 58 yo, Cauc.	9	Bloating	Mild	Resolved
Study 851-CR1 (Placebo)					
102-20	F, 50 yo, Cauc.	3 – 4	Abdominal cramping Heartburn (dyspepsia)	Mild	Resolved
108-12	F, 47 yo, Cauc.	69 – 152	Breast carcinoma	Severe	Hospitalized for treatment/ resolved with sequelae
113-4	F, 75 yo, Cauc.	28	Anemia	Severe	Unresolved. Later diagnosed with gastric cancer
117-6	F, 52 yo, AA	94	Worsening abdominal pain	Moderate	Pain unresolved. Diagnosed with cancer of sigmoid.
119-8	F, 33yo, Cauc.	124	Diarrhea	Moderate	Resolved
134-12	F, 51 yo, Cauc.	134 – 154	Bilateral lower lobe pneumonia	Moderate	Resolved
136-9	F, 64 yo, Cauc.	8 – 21	Nausea	Mild	Resolved

Table 5: Subject discontinuations due to adverse events in Studies 851-CR1, 851-ZCC, and 851-CR3

Subject	Demographics	Study Days	Adverse Event	Severity	Outcome
Study 851-ZCC (MiraLax): none					
Study 851-ZCC (Zelnorm)					
102-5	F, 48 yo, AA	3 – 10	Diarrhea, Nausea Headache	Moderate Mild	Resolved
120-4	M, 41 yo, Cauc.	23	Abdominal pain Diarrhea, Headache	Moderate Moderate	Abdominal pain unresolved
146-1	F, 19 yo, Cauc.	13	Abdominal pain	Mild	Unresolved
148-4	F, 53 yo, Cauc.	2 – 12	Increased sweating and urination	Moderate	Resolved
153-12	M, 61 yo, Cauc.	10	Anal pain and burning	Severe	Unresolved
Study 851-CR3 (MiraLax)					
103-98	M, 46 yo, Cauc.	42 – 77	Left abdominal pain	Moderate	Resolved
108-8	M, 38 yo, Cauc.	1	Hypothyroidism		
109-237	M, 75 yo, Cauc.	0 – 133	Loose stools	Moderate	Resolved
111-15	M, 55 yo, ?	11 - 14 21 – 26	Abdominal discomfort	Moderate	Resolved
114-216	F, 33yo, Cauc.	11 – 57	Worsening abdominal cramps and nausea	Mild	Resolved
117-2	F, 48 yo, AA	1	Vasovagal episode	Moderate	Resolved
123-220	F, 56 yo, Cauc.	56 – 78	Abscess, descending colon	Severe	Resolved with treatment
124-110	F, 58 yo Cauc.	2 – 6	Abdominal bloating and swelling of extremities	Moderate	Resolved
127-248	F, 62 yo, Cauc.	Chronic 20 – 50 111 – 115	Depression Indigestion Upper respiratory infection	Moderate Severe Mild	Depression unresolved
127-249	F, 65 yo, Cauc.	15 – 29	Diarrhea	Moderate	Resolved
130-434	F, 54 yo, Cauc.	187	Upper abdominal pain	Mild	Unresolved
134-147	F, 63 yo, Cauc.	1	Abnormal TSH level	Moderate	
135-198	F, 68 yo, Cauc.	91 91 - 105	Indigestion, Flatulence, nausea, Indigestion Black stool Diarrhea	Moderate Mild Moderate Moderate Moderate	Resolved. Dose decreased with initial indigestion episode
137-33	M, 37 yo, Cauc.	57	Increased SGPT (ALT)	Moderate	Unresolved
139-192	F, 58 yo, Cauc.	101	Fecal incontinence	Not specified	Resolved
140-207	F, 25 yo, Cauc.	1 46 – 50	Hematuria Sore throat	Moderate Mild	Hematuria unresolved
142-269	F, 53 yo, Cauc.	46 – 50	Diarrhea Vomiting	Moderate	Resolved
144-167	F, 51 yo, Hispanic	105	Watery stools	Moderate	Unresolved
146-44	M, 33 yo, Cauc.	4 – 26	Diarrhea	Moderate	Resolved
146-47	F, 59 yo, Cauc.	5 – 38	Frequent BMs	Mild	Had reduced dose to 8.5g/day prior to D/C. Resolved

Table 5: Subject discontinuations due to adverse events in Studies 851-CR1, 851-ZCC, and 851-CR3					
Subject	**Demographics**	**Study Days**	**Adverse Event**	**Severity**	**Outcome**
146-48	F, 25 yo, Cauc.	3 – 73 74 – 83	Increased flatulence	Mild Moderate	Resolved
149-402	M, 86 yo, Cauc.	154 – 158	Acute diarrhea Anemia Dehydration	Severe	Resolved
150-122	F, 28 yo, AA	182 – 243	Increased flatulence	Mild	Resolved

7.1.3.3 Other significant adverse events

During Studies 851-CR1, 851-CR3, and 851-ZCC, 635 subjects used MiraLax and 53 (8.4%) reduced their dose of MiraLax temporarily or permanently due to an adverse event. Study investigators reduced the daily MiraLax dose in 16 of 204 subjects in Study 851-CR1, 33 of 311 subjects in Study 851-CR3, and four of 120 subjects in Study 851-ZCC. Reduced doses of MiraLax were: 4.3 - 8.5 g QD or 8.5 - 17 g QOD. This reviewer was not able to locate case report forms (CRFs) for subjects with reductions in dose in the NDA submission. Upon request, the sponsor sent in copies of the case report forms missing from Studies 851-CR1 and 851-ZCC (except for the CRF for subject 130-11 from Study 851-CR1). The reduced MiraLax dose could not be determined for eight subjects from Studies 851-CR1 and 851-ZCC or for any subjects from 851-CR3. The missing CRFs from Study 851-CR3 have also been requested. Below, Table 6 provides a summary of precipitating adverse events that resulted in temporary or permanent reductions in MiraLax dose. A detailed line listing of all subjects with MiraLax dose reductions may be found in the Appendix 10.3 under *Other Pertinent Information.*

Table 6: Summary of adverse events that resulted in temporary or permanent MiraLax dose reductions*	
Precipitating Adverse Event	**Subjects (N = 53) N(%)**
Diarrhea	23 (43.4)
Loose stools	9 (17.0)
Flatulence/increased gas	8 (15.1)
Abdominal pain/cramping	6 (11.3)
Abdominal distension/bloating	3 (5.7)
Nausea	3 (5.7)
Fecal urgency	2 (3.8)
Fecal incontinence/leakage	2 (3.8)
Gastroenteritis	1 (1.9)

* A detailed line listing of subjects with MiraLax dose reductions is in Appendices under Other Pertinent Information.

Based on information available in the submitted adverse event tables and the study protocols, it appears that study investigators based dose reduction decisions on their own clinical judgement. Most dose reductions followed episodes of watery stools, diarrhea, abdominal cramping, and/or increased flatulence; however, a wide range of symptom severity and duration prompted dose reduction with some study sites reducing dose more readily and more often.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Historically, common drug-related adverse events associated with laxative use include:

- Diarrhea or loose stools
- Abdominal cramping
- Flatulence
- Abdominal bloating.

Consistent with these known effects of laxative use, the prescription labeling for MiraLax states:

> *Nausea, abdominal bloating, cramping, and flatulence may occur. High doses may product diarrhea and excessive stool frequency, particularly in elderly nursing home patients.*
>
> *Patients taking other medications containing polyethylene glycol have occasionally developed urticaria suggestive of an allergic reaction.*

7.1.5.1 Eliciting adverse events data in the development program

In each of the three clinical studies, study personnel used the same adverse events table sheet to document adverse events reported by study participants. Study investigators and staff performed physical exams at the enrollment visit and at the final study visit and measured vital signs at each study visit. The daily IVRS system did not provide a mechanism through which study subjects could record adverse events other than those related to hard or lumpy stool; loose, watery stools; extreme gas and/or extreme abdominal cramping. The study visit sheets used to record information at each study visit provided a place to note whether the subject had experienced any adverse events since the last visit

and what the reaction was. The visit sheet then referred the recorder to the adverse event sheet. The adverse event sheet provided places to record the following information about each event: description, onset date, stop date, whether the event was ongoing, severity, relationship to study drug, treatment, outcome, and whether or not the event was serious. However, the study subjects did not have a diary to use at home to record adverse events as they occurred. The study protocols did not describe whether study personnel instructed subjects to report adverse events by phone as they occurred.

Reviewer comment:

Subjects may have reported the majority of their adverse events retrospectively over 28 – 90 days. It is not clear how this influenced the accuracy of reporting. Subjects in study 851-CR1 had monthly visits to the study center. Subjects in study 851-CR3 had study visits at months 2, 4, 6, 9, and 12. Subjects in study 851-ZCC visited the study center only at enrollment and at the end of the study (28 days of treatment).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse event reports were categorized using MedDRA preferred terms and categories.

7.1.5.3 Incidence of common adverse events

In Study 851-CR1, there were no treatment emergent differences between treatment groups over the six months study except for gastrointestinal (GI) adverse events (AEs) where 40% of MiraLax subjects experienced at least one GI AE compared to 25% of placebo treated subjects. Most reports of diarrhea were based on IVRS reports of three or more stools per day rather than the protocol definition of diarrhea (three consecutive days of three or more loose, watery stools). Among individual GI AEs, there were no statistically significant differences between treatment groups. The greatest differences in AE incidence were seen with diarrhea, flatulence, loose stools, and nausea. Most GI AEs were mild to moderate in intensity, although five MiraLax subjects and one placebo subject experienced a severe GI AE. Detailed tables comparing incidences of adverse event rates between treatment groups may be found in section 7.1.5.4 below.

In addition, Table 7 below describes adverse events among subjects in the pharmacokinetic (PK) studies submitted in support of this NDA. A line listing of adverse events by subject was not provided for all PK studies.

Table 7: Adverse Events Among Pharmacokinetic Study Subjects		
Study	**Type of Study**	**Adverse Events**
Pharmacokinetic studies		
851-PK-001	Single dose PK Healthy volunteers (N = 6)	None
851-PK-002 (N = 14)	Multiple dose PK (7 days) Healthy volunteers	No serious adverse events. The following subjects reported constipation: Subject 1: Days 3 and 7 Subject 3: Day 2 Subject 5: Day 1 Subject 8: Day 1 Subject 9: Day 1 The following subjects reported headache: Subject 1: Day 5 Subject 9: Days 2, 3, and 4 Other adverse events: Subject 4: bilateral hip pain (Day 4) Subject 7: punctured skin (Day 3) Subject 9: nausea (Days 2, 3, 4) One subject reported 6 episodes of loose stool; however, these episodes were not listed as adverse events in the study's adverse event table.
851-PK-004	Open-label, multiple dose PK, Six patients with ESRD Six age, weight, and gender matched controls (Dialysate from these subjects used for study 851-PK-006)	Three of six patients with ESRD experienced at least one adverse event. One ESRD patient, Subject 3, experienced a serious adverse event following discharge from the study when he 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. This SAE was deemed unrelated to study drug. Other adverse events among ESRD patients included: Subject 2: bloating, nasal congestion (both mild) Subject 3: stomach cramps, bloating (2), gas, chest pain shortness of breath (2), headache Subject 4: heartburn, dyspepsia, loose stools. Four of six normal, matched control subjects experienced at least one adverse event during the study: Subject 6: headache Subject 7: headache, diarrhea, upset stomach Subject 9: upper respiratory infection (cold) Subject 10: headache (2), lightheadedness.
851-PK-005	Open-label, multiple dose PK 24 healthy volunteers (7 days) (Volume 7)	No serious adverse events. 13 of 24 subjects experienced a total of 44 adverse events. Twenty-three events were considered possibly related to study drug, but none were considered probably or likely related. Three reports of constipation in two subjects; six reports of constipation in two subjects, three subjects who each experienced one episode of nausea, six episodes of abdominal pain or cramping in five subjects, and one episode of abdominal bloating. None of the events were severe and only two were moderate.

7.1.5.4 Common adverse event tables

Table 8 displays adverse event data for the two safety and efficacy studies (851-CR1 and 851-ZCC) and one long term safety study (851-CR3). To facilitate comparisons of adverse event incidence between treatment groups and across studies of different durations, the table includes information on study duration, the percentage of subjects who experienced any adverse event, the total number of AEs, and the percentage of subjects in each treatment group who experienced one or more AE for each MedDRA body system. Body systems are included if such an AE was experienced by 1% or more of subjects in any listed treatment group. Study 851-CR1 was the only double-blind, placebo-controlled study. Inclusion and exclusion criteria for the three studies were identical, so while the studies were of varying duration and were not all placebo-controlled, the combined table provides an opportunity to view adverse event incidences for a total of 635 MiraLax treated subjects and 100 placebo treated subjects.

Table 8: Studies 851-CR1, 851-CR3, and 851-ZCC: Treatment Emergent Adverse Events by MedDRA Body System with Incidence > 1% in at least one treatment group

Adverse Events	851-CR1			851-CR3	851-ZCC
	Placebo (N = 100)	MiraLax (N = 204)	P-value	MiraLax (N = 311)	MiraLax (N = 120)
Duration of study	6 months			12 months	28 days
Patients with events	57%	69%		67%	33%
Number of events	127	359	0.055	619	76
Body system	% subjects			% subjects	% subjects
Blood/lymphatic	3.0	0.5	0.106	1.3	0
Cardiac	0	1.5	0.553	1.3	0
Ear/labyrinth	0	2.0	0.307	2.3	0.8
Endocrine	0	0.5	1.000	1.0	0
Eye	0	0.5	1.000	1.6	0
Gastrointestinal	25.0	39.7	**0.015**	35.7	30.8
General disorders, administrations	4.0	6.9	0.107	4.2	0
Immune system	2.0	0	0.440	1.6	0
Infection/infestation	19.0	23.5	0.462	26.0	3.3
Injury, poisoning	5.0	4.4	0.779	5.8	0
Investigations	9.0	5.4	0.324	7.7	0
Metabolism/nutrition	3.0	2.9	1.000	2.6	0.8
Musculoskeletal	7.0	10.8	0.406	13.2	0.8
Neoplasms	3.0	1.5	0.399	1.0	0.8
Nervous system	4.0	4.4	1.000	9.6	0.8
Psychiatric	4.0	3.9	1.000	5.8	0
Renal/urinary	2.0	0	0.107	1.6	1.7
Reproductive/breast	0	1.5	0.553	2.9	0
Respiratory, thoracic, mediastinal	3.0	6.4	0.281	9.0	0.8
Skin, subcutaneous	1.0	3.9	0.280	4.2	0.8
Surgical and medical procedures	0	1.0	1.000	4.5	0.8
Vascular	2.0	2.5	1.000	3.5	0

7.1.5.5 Identifying common and drug-related adverse events

Except for GI adverse events, the investigators considered most AEs unrelated to MiraLax treatment. As shown in Table 9 below, there were only two non-GI adverse events considered probably related to MiraLax use and 35 AEs considered possibly related to MiraLax use.

Table 9: Incidence of adverse events, by MedDRA Body System, among subjects treated with placebo and MiraLax and their relationship to study drug (includes data from Studies 851-CR1, 851-CR3, 851-ZCC)

MedDRA Body System	Placebo (N = 100) N and %	MiraLax (N = 635)				
		All AEs N (%)	Relationship to MiraLax treatment			
			None	Possible	Probable	Definite
Patients with events	57	389 (61.3)	197 (31.0)	76 (12.0)	91 (14.3)	25 (3.9)
Number of events	127	1054	703	162	156	33
Blood/lymphatic	3	5 (0.8)	4 (0.6)	**1 (0.2)**	0	0
Cardiac disorders	0	7 (1.1)	6 (0.9)	**1 (0.2)**	0	0
Congenital, familial, genetic	0	1 (0.2)	1 (0.2)	0	0	0
Ear/labyrinth	0	12 (1.9)	12 (1.9)	0	0	0
Endocrine	0	4 (0.6)	2 (0.3)	**2 (0.3)**	0	0
Eye	0	6 (0.9)	6 (0.9)	0	0	0
Gastrointestinal	25	229 (36.1)	54 (8.5)	**60 (9.4)**	**90 (14.2)**	**25 (3.9)**
General disorders, administrations	4	27 (4.3)	24 (3.8)	**3 (0.5)**	0	0
Hepatobiliary	0	2 (0.3)	2 (0.3)	0	0	0
Immune system	2	5 (0.8)	5 (0.8)	0	0	0
Infection/infestation	19	133 (20.9)	131 (20.6)	**2 (0.3)**	0	0
Injury, poisoning, procedural	5	27 (4.3)	27 (4.3)	0	0	0
Investigations	9	35 (5.5)	23 (3.8)	**10 (1.6)**	**1 (0.2)**	0
Metabolism/nutrition	3	15 (2.4)	11 (1.7)	**4 (0.6)**	0	0
Musculoskeletal	7	64 (10.1)	62 (9.8)	**2 (0.3)**	0	0
Neoplasms	3	7 (1.1)	7 (1.1)	0	0	0
Nervous system	4	40 (6.3)	36 (5.7)	**4 (0.6)**	0	0
Pregnancy, puerperium, perinatal	0	1 (0.2)	1 (0.2)	0	0	0
Psychiatric	4	26 (4.1)	26 (4.1)	0	0	0
Renal/urinary	2	7 (1.1)	7 (1.1)	0	0	0
Reproductive/breast	0	12 (1.9)	11 (1.7)	**1 (0.2)**	0	0
Respiratory, thoracic, mediastinal	3	42 (6.6)	40 (6.3)	**1 (0.2)**	**1 (0.2)**	0
Skin, subcutaneous	1	22 (3.5)	18 (2.8)	**4 (0.6)**	0	0
Social circumstances	0	1 (0.2)	1 (0.2)	0	0	0
Surgical and medical procedures	0	17 (2.7)	17 (2.7)	0	0	0
Vascular	2	16 (2.5)	15 (2.4)	**1 (0.2)**	0	0

Reviewer Comment

Only 50% of GI adverse events were considered probably or definitely related to MiraLax treatment. Subjects with constipation may experience GI adverse events that overlap symptoms that classically accompany laxative use. In addition, subjects in all three studies (including those on placebo) were allowed to use bisacodyl as a rescue laxative. GI symptoms associated in time with rescue laxative use are more likely related to bisacodyl than MiraLax.

In the placebo-controlled trial (851-CR1), there was a statistically higher incidence of GI adverse events among subjects treated with MiraLax compared to those treated with placebo (Table 10). However, there were no statistically significant differences between treatment groups for individual GI adverse events. The greatest differences in incidence occurred with diarrhea, flatulence, loose stools, and nausea, with higher incidences among MiraLax users. The increased incidence of flatulence among MiraLax users nearly reached statistical significance.

Table 10: Study 851-CR1: Gastrointestinal(GI) adverse events occurring in >1% of subjects

GI Adverse Event	MiraLax (%) (N = 204)	Placebo (%) (N = 100)	P-value
Diarrhea	17.2	11.0	0.177
Loose stools	7.8	3.0	0.131
Flatulence	7.4	2.0	0.065
Nausea	5.9	1.0	0.329
Abdominal distension	4.9	1.0	0.109
Abdominal pain NOS	1.5	3.0	0.399
Abdominal pain, upper	0.5	3.0	0.106
Dyspepsia	0.5	3.0	0.106
Vomiting	2.0	0	0.307

Most GI adverse events were mild to moderate in intensity. As shown in Table 11 below, five MiraLax subjects and one placebo subject experienced one or two severe GI adverse events; the remainder were mild or moderate in intensity.

Table 11: Severe GI adverse events among subjects in Study 851-CR1

Adverse Event	Subjects N (% population)	Treatment
Abdominal distension	2 (1%)	MiraLax
Diarrhea	2 (1%)	MiraLax
Flatulence	2 (1%)	MiraLax
Loose stools	1 (1%)	Placebo

Table 12 presents the numbers and percentages of MiraLax treated subjects from Studies 851-CR1, 851-CR3, and 851-ZCC that experienced GI AEs and divides them by symptom severity. Out of 635 MiraLax subjects, 229 experienced 340 GI AEs, and of those, 17 were severe. These severe cases included: 6 cases of abdominal distension, 4 cases of diarrhea, one case of dyspepsia, 2 cases of flatulence, 1 case of hemorrhoids, 1 esophageal perforation, 1 rectal disorder, and one toothache.

Table 12: Subjects using MiraLax (N = 635) with GI adverse events listed by severity and MedDRA Preferred Term

MedDRA Preferred Term	MiraLax treated subjects with GI AE(s)			
	Total N(%)	Mild N(%)	Moderate N(%)	Severe N(%)
Abdominal discomfort	3 (0.5)	1 (0.2)	2 (0.3)	0
Abdominal distension	21 (3.3)	9 (1.4)	6 (0.9)	6 (0.9)
Abdominal pain NOS	13 (2.0)	5 (0.8)	8 (1.3)	0
Abdominal pain lower	4 (0.6)	3 (0.5)	1 (0.2)	0
Abdominal pain upper	7 (1.1)	5 (0.8)	2 (0.3)	0
Abdominal tenderness	8 (1.3)	8 (1.3)	0	0
Anal discomfort	1 (0.2)	1 (0.2)	0	0
Anal skin tags	1 (0.2)	1 (0.2)	0	0
Barrett's esophagus	1 (0.2)	1 (0.2)	0	0
Colonic polyp	1 (0.2)	1 (0.2)	0	0
Constipation	1 (0.2)	0	1 (0.2)	0
Defecation urgency	3 (0.5)	1 (0.2)	2 (0.3)	0
Diarrhea NOS	92 (14.5)	55 (8.7)	33 (5.2)	4 (0.6)
Diverticulitis NOS	2 (0.3)	2 (0.3)	0	0
Dry mouth	1 (0.2)	1 (0.2)	0	0
Dyspepsia	7 (1.1)	3 (0.5)	3 (0.5)	1 (0.2)
Dysphagia	1 (0.2)	0	1 (0.2)	0
Fecal incontinence	4 (0.6)	3 (0.5)	1 (0.2)	0
Feces discolored	2 (0.3)	1 (0.2)	1 (0.2)	0
Flatulence	40 (6.3)	26 (4.1)	12 (1.9)	2 (0.3)
Frequent bowel movements	6 (0.9)	3 (0.5)	3 (0.5)	0
Gastric ulcer	1 (0.2)	0	1 (0.2)	0
Gastritis NOS	4 (0.6)	1 (0.2)	3 (0.5)	0
GI motility disorder NOS	1 (0.2)	1 (0.2)	0	0
GI pain NOS	1 (0.2)	1 (0.2)	0	0
Gastroesophageal reflux disease	5 (0.8)	4 (0.6)	1 (0.2)	0
Gingival pain	1 (0.2)	0	1 (0.2)	0
Glossodynia	1 (0.2)	1 (0.2)	0	0
Hemorrhoidal hemorrhage	1 (0.2)	0	1 (0.2)	0
Hemorrhoids	6 (0.9)	2 (0.3)	3 (0.5)	1 (0.2)
Lip dry	1 (0.2)	1 (0.2)	0	0
Loose stools	28 (4.4)	18 (2.8)	10 (1.6)	0
Melaena	1 (0.2)	1 (0.2)	0	0
Nausea	34 (5.4)	23 (3.6)	11 (1.7)	0
Esophageal perforation	1 (0.2)	0	0	1 (0.2)
Parotid duct obstruction	1 (0.2)	1 (0.2)	0	0
Periodontitis	1 (0.2)	1 (0.2)	0	0

Table 12: Subjects using MiraLax (N = 635) with GI adverse events listed by severity and MedDRA Preferred Term

MedDRA Preferred Term	MiraLax treated subjects with GI AE(s)			
	Total N(%)	Mild N(%)	Moderate N(%)	Severe N(%)
Peritoneal cyst	1 (0.2)	1 (0.2)	0	0
Proctalgia	1 (0.2)	1(0.2)	0	0
Pruritis ani	4 (0.6)	3 (0.5)	1 (0.2)	0
Rectal disorder NOS	3 (0.5)	2 (0.3)	0	1 (0.2)
Rectal hemorrhage	3 (0.5)	3 (0.5)	0	0
Stomatitis	1 (0.2)	0	1 (0.2)	0
Stools watery	4 (0.6)	0	4 (0.6)	0
Swollen tongue	1 (0.2)	1 (0.2)	0	0
Tooth impacted	1 (0.2)	0	1 (0.2)	0
Toothache	4 (0.6)	2 (0.3)	1 (0.2)	1 (0.2)
Vomiting NOS	10 (1.6)	6 (0.9)	4 (0.6)	0
Totals	340	204	119	17

In Studies 851-CR1 and 851-CR3, there were 46 subjects who reported "significant diarrhea" on two or more consecutive days. With the exception of injuries, subjects on MiraLax who experienced "significant diarrhea" did not experience higher incidences of non-diarrhea adverse events compared to subjects using MiraLax who did not experience diarrhea. The increased incidence of injuries in the diarrhea group was attributable to slightly higher rates of sprains, fractures, and whiplash injuries with low actual numbers of cases (one or two in each group). As will be discussed in the laboratory findings portion of the review (Section 7.1.7), subjects with "significant diarrhea" did not have more frequent or more extreme abnormal chemistry, hematology, or urinalysis results compared to baseline values.

7.1.5.6 Additional analyses and explorations

The sponsor did not submit data on dose ranging in support of this application as they completed 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.

The sponsor did provide data analyses exploring 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.

7.1.5.6.1 Effect of duration of use on adverse event incidence

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 13 displays the adverse event rates by body system and study segment.

Table 13: 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:

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).*

7.1.5.6.2 Effect of advanced age on adverse event incidence

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.

The elderly subpopulation in Study 851-CR1 consisted of 75 individuals ages 65 years and older. For the elderly cohort, there were no statistically significant differences between MiraLax and placebo treatment groups in incidences of adverse events by body system; however, the small sample sizes of this comparison should be noted. Overall incidences of adverse events by MedDRA body system (including GI) were similar to those seen in the the general study population. Table 14 compares the incidence of adverse events among elderly subjects treated with MiraLax and those treated with placebo. There are no statistically significant differences between treatment groups; however the study groups are small. Compared to MiraLax-treated subjects, the placebo-treated elderly subjects have a numerically greater incidence of blood/lymphatic system adverse events and investigation-associated adverse events.

Table 14: Study 851-CR1: Elderly Subjects (Age ≥ 65) with treatment emergent adverse events by MedDRA body system with incidence > 1%

Body system	MiraLax (N = 51)	Placebo (N = 24)	P-value
Patients with events	71%	54%	0.198
Number of events	80	34	
Blood/lymphatic	0	8.3%	0.099
Cardiac disorders	2.0%	0	1.000
Ear/labyrinth	3.9%	0	1.000
Gastrointestinal	31.4%	25.0%	0.786
General disorders and administration	7.8%	4.2%	1.000
Infection/infestation	17.6%	8.3%	0.486
Investigations	3.9%	16.7%	0.079
Metabolism/nutrition	2.0%	8.3%	0.238
Musculoskeletal	9.8%	8.3%	1.000
Neoplasms	3.9%	4.2%	1.000
Nervous system	7.8%	8.3%	1.000
Psychiatric	5.9%	4.2%	1.000
Respiratory, thoracic, mediastinal	2.0%	0%	1.000
Skin, subcutaneous	7.8%	0	0.299
Surgical and medical procedures	2.0%	0	1.000
Vascular	7.8%	0	0.299

Data from Study 851-CR3, shown below in Table 15, shows that elderly and non-elderly subjects experienced similar rates of adverse events by body systems during the study.

Table 15: Comparison of adverse event (AE) rates in the elderly and non-elderly subpopulations in Study 851-CR3

Adverse Events	All subjects (N = 311)	Elderly (N = 117)	Non-elderly (N = 194)
Patients with events	209 (67.2%)	82 (70.1%)	127 (65.5%)
Number of events	619	241	378
MedDRA Body System		**N(%)**	**N (%)**
Blood/lymphatic	4 (1.3)	3 (2.6)	1 (0.5)
Cardiac disorders	4 (1.3)	1 (0.9)	3 (1.5)
Congenital, familial, genetic	1 (0.3)	0	1 (0.5)
Ear/labyrinth	7 (2.3)	2 (1.7)	5 (2.6)
Endocrine	3 (1.0)	1 (0.9)	2 (1.0)
Eye	5 (1.6)	2 (1.7)	3 (1.5)
Gastrointestinal	111 (35.7)	47 (40.2)	64 (33.0)
General disorders, administrations	13 (4.2)	4 (3.4)	9 (4.6)
Hepatobiliary	1 (0.3)	1 (0.9)	0
Immune system	5 (1.6)	1 (0.9)	4 (2.1)
Infection/infestation	81 (26.0)	32 (27.4)	49 (25.3)
Injury, poisoning, procedural	18 (5.8)	8 (6.8)	10 (5.2)
Investigations	24 (7.7)	8 (6.8)	16 (8.2)
Metabolism/nutrition	8 (2.6)	5 (4.3)	3 (1.5)
Musculoskeletal	41 (13.2)	19 (16.2)	2 (11.3)
Neoplasms	3 (1.0)	1 (0.9)	2 (1.0)
Nervous system	30 (9.6)	13 (11.1)	17 (8.8)
Pregnancy, puerperium, perinatal	1 (0.3)	0	1 (0.5)
Psychiatric	18 (5.8)	3 (2.6)	15 (7.7)
Renal/urinary	5 (1.6)	3 (2.6)	2 (1.0)
Reproductive/breast	9 (2.9)	1 (0.9)	8 (4.1)
Respiratory, thoracic, mediastinal	28 (9.0)	13 (11.1)	15 (7.7)
Skin, subcutaneous	13 (4.2)	5 (4.3)	8 (4.1)
Surgical and medical procedures	14 (4.5)	7 (6.0)	7 (3.6)
Vascular	11 (3.5)	4 (3.4)	7 (3.6)

Table 16 compares the relative incidences of GI adverse events in the 851-CR1 study population as a whole and for the elderly cohort by study treatment. The table also includes GI adverse event rates for the elderly and general study populations for Study 851-CR3.

Table 16: Study 851-CR1: Comparison of incidences of more common GI adverse events between the elderly cohort and the study population as a whole

GI Preferred Term	Study 851-CR1				Study 851-CR3 MiraLax N(%)	
	Placebo N(%)		MiraLax N(%)			
	All* (N = 100)	Elderly* (N = 24)	All* (N = 204)	Elderly* (N = 51)	All (N = 311)	Elderly (N = 117)
Abdominal distension	1 (1.0)	0	10 (4.9)	1 (2.0)	9 (2.9)	1 (0.9)
Abdominal pain NOS	3 (3.0)	0	3 (1.5)	0	8 (2.6)	2 (1.7)
Abdominal pain upper	3 (3.0)	1 (4.2)	1 (0.5)	1 (2.0)	5 (1.6)	1 (0.9)
Defecation urgency	0	0	2 (1.0)	1 (2.0)	1 (0.3)	1 (0.9)
Diarrhea NOS	11 (11.0)	3 (12.5)	35 (17.2)	9 (17.6)	33 (10.6)	15 (12.8)
Dyspepsia	3 (3.0)	1 (4.2)	1 (0.5)	0	6 (1.9)	3 (2.6)
Flatulence	2 (2.0)	0	15 (7.4)**	2 (3.9)	23 (7.4)	10 (8.5)
Loose stools	3 (3.0)	1 (4.2)	16 (7.8)	3 (5.9)	12 (3.9)	5 (4.3)
Nausea	1 (1.0)	0	12 (5.9)	2 (3.9)	17 (5.5)	8 (6.8)
Rectal disorder NOS	0	0	1 (0.5)	1 (2.0)	2 (0.6)	2 (1.7)
Rectal hemorrhage	1 (1.0)	1 (4.2)	0	0	2 (0.6)	2 (1.7)
Vomiting	0	0	4 (2.0)	1 (2.0)	6 (1.9)	2 (1.7)

* There were no statistically significant differences in incidences of individual GI adverse events between active and placebo treatment groups for their respective population subgroups.
**For the study population as a whole, the increased incidence of flatulence in the MiraLax treated group approached statistical significance with p = 0.065.

Overall, the elderly subjects treated with MiraLax did not experience greater incidences of GI adverse events or other adverse events by body system or compared to the study population as a whole. The more common GI adverse events experienced by elderly subjects in Studies 851-CR1 and 851-CR3 were no more severe than those of the general population overall. This is illustrated in Table 17.

Table 17: Comparison of GI adverse event incidence and severity between the elderly and general populations for more common GI AEs (Studies 851-CR1 and 851-CR3)

GI Preferred Term	All MiraLax Subjects (N = 515) N (%)			Elderly MiraLax Subjects (N = 141) N (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
All GI disorders	97 (18.8)	82 (15.9)	13 (2.5)	30 (21.3)	29 (20.6)	4 (2.8)
Abdominal distension	9 (1.7)	6 (1.2)	4 (0.8)	1 (0.7)	1 (0.7)	0
Abdominal pain NOS	4 (0.8)	7 (1.4)	0	1 (0.7)	1 (0.7)	0
Diarrhea NOS	33 (6.4)	32 (6.2)	3 (0.6)	8 (5.7)	14 (9.9)	2 (1.4)
Flatulence	22 (4.3)	13 (2.5)	3 (0.6)	8 (5.7)	3 (2.1)	1 (0.7)
Loose stools	18 (3..5)	10 (1.9)	0	5 (3.5)	3 (2.1)	0
Nausea	19 (3.7)	10 (1.9)	0	9 (6.4)	0	0

7.1.5.6.3 Effects of gender and race/ethnicity on adverse event incidence

In Studies 851-CR1 and 851-CR3, there were 103 males and 121 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. This information and additional adverse event rate details are displayed below in

Table 18.

Table 18: Comparison of adverse event (AE) rates: male vs. female subpopulations and non-Caucasian vs. Caucasian subpopulations (Studies 851-CR1 and 851-CR3, N = 635)

Adverse Events	Male (N = 103)	Female (N = 532)	Non-Caucasian (N = 121)	Caucasian (N = 514)
Patients with events	70 (68.0%)	319 (60.0%)	60 (49.6%)	334 (65.0%)
Number of events	162	892	139	934
MedDRA Body System	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Blood/lymphatic	1 (1.0)	4 (0.8)	0	5 (1.0)
Cardiac disorders	0	7 (1.3)	0	7 (1.4)
Congenital, familial, genetic	0	1 (0.2)	1 (0.8)	0
Ear/labyrinth	1 (1.0)	11 (2.1)	2 (2.7)	10 (1.9)
Endocrine	0	4 (0.8)	1 (0.8)	3 (0.6)
Eye	0	6 (1.1)	1 (0.8)	6 (1.2)
Gastrointestinal	36 (35.0)	193 (36.3)	34 (28.1)	199 (38.7)
General disorders, administrations	4 (3.9)	23 (4.3)	5 (4.1)	22 (4.3)
Hepatobiliary	0	2 (0.4)	1 (0.8)	1 (0.2)
Immune system	0	5 (0.9)	1 (0.8)	4 (0.8)
Infection/infestation	19 (18.4)	114 (21.4)	15 (12.4)	118 (23.0)
Injury, poisoning, procedural	1 (1.0)	26 (4.9)	3 (2.5)	24 (4.7)
Investigations	9 (8.7)	26 (4.9)	7 (5.8)	35 (6.6)
Metabolism/nutrition	3 (2.9)	12 (2.3)	2 (1.7)	13 (2.5)
Musculoskeletal	16 (15.5)	48 (9.0)	13 (10.7)	51 (9.9)
Neoplasms	3 (2.9)	4 (0.8)	3 (2.5)	5 (1.0)
Nervous system	11 (10.7)	29 (5.5)	6 (5.0)	35 (6.8)
Pregnancy, puerperium, perinatal	0	1 (0.2)	4 (3.3)	1 (0.2)
Psychiatric	2 (1.9)	24 (4.5)	4 (3.3)	22 (4.3)
Renal/urinary	0	7 (1.3)	0	9 (1.8)
Reproductive/breast	0	12 (2.3)	2 (1.7)	12 (2.3)
Respiratory, thoracic, mediastinal	9 (8.7)	33 (6.2)	8 (6.6)	34 (6.6)
Skin, subcutaneous	3 (2.9)	19 (3.6)	2 (1.7)	20 (3.9)
Social circumstances	0	1 (0.2)	0	1 (0.2)
Surgical and medical procedures	4 (3.9)	13 (2.4)	2 (1.7)	15 (2.9)
Vascular	5 (4.9)	11 (2.1)	2 (1.7)	14 (2.7)

Females had a numerically higher incidence of infections in 851-CR1 (25.7%) than males (10.3%), mostly due to differences in the incidences of urinary tract infections and upper respiratory infections but this difference was not seen in 851-CR3, which had a larger MiraLax-treated population. Numerically, Caucasians experienced more GI adverse events than non-Caucasians (39% vs. 28%). Most of this difference was due to numerically higher incidences of diarrhea (16% vs. 11%). The following tables (Tables 19 and 20) show the severity of the most common GI adverse events in these subpopulations. There were no significant differences in adverse event severity among these subpopulations.

Table 19: Comparison of GI adverse event severity between the male and female subpopulations for more common GI AEs (Studies 851-CR1 and 851-CR3)

GI Preferred Term	Male MiraLax Subjects (N = 103)			Female MiraLax Subjects (N = 532)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
All GI disorders	19 (18.4)	15 (14.6)	2 (1.9)	120 (22.6)	63 (11.8)	10 (1.9)
Abdominal distension	0	2 (1.9)	1 (1.0)	9 (1.7)	4 (0.8)	5 (0.9)
Abdominal pain NOS	0	1 (1.0)	0	5 (0.9)	7 (1.3)	0
Diarrhea NOS	5 (4.9)	6 (5.8)	1 (1.0)	50 (9.4)	27 (5.1)	3 (0.6)
Flatulence	3 (2.9)	5 (4.9)	0	23 (4.3)	7 (1.3)	2 (0.4)
Loose stools	3 (2.9)	2 (1.9)	0	15 (2.8)	8 (1.5)	0
Nausea	3 (2.9)	1 (1.0)	0	20 (3.8)	10 (1.9)	0

Table 20: Comparison of GI adverse event severity between the non-Caucasian and Caucasian subpopulations for more common GI AEs (Studies 851-CR1 and 851-CR3)

GI Preferred Term	Non-Caucasian MiraLax Subjects (N = 121)			Caucasian MiraLax Subjects (N = 514)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
All GI disorders	20 (16.5)	13 (10.7)	1 (0.8)	123 (24.0)	65 (12.6)	11 (2.1)
Abdominal distension	0	1 (0.8)	1 (0.8)	8 (1.6)	5 (1.0)	5 (1.0)
Abdominal pain NOS	0	1 (0.8)	0	5 (1.0)	7 (1.4)	0
Diarrhea NOS	9 (7.4)	4 (3.3)	0	46 (9.0)	30 (5.8)	4 (0.8)
Flatulence	4 (3.3)	2 (1.7)	0	222 (4.3)	10 (1.9)	2 (0.4)
Loose stools	3 (2.5)	0	0	15 (2.9)	10 (1.9)	0
Nausea	3 (2.5)	1 (0.8)	0	20 (3.9)	10 (1.9)	0

7.1.5.6.4 Adverse events among high risk vs. non-high risk subjects
The sponsor defined a *high risk* subject as one with a medical history of heart problems, kidney problems and/or diabetes. Subjects from Study 851-ZCC were not included in this analysis because elderly females and all males were excluded from enrollment following a protocol amendment. Studies 851-CR1 and 851-CR3 enrolled a total of 99 subjects who met the *high risk* definition.

In Study 851-CR3, *high risk* subjects (N = 70) experienced statistically higher adverse event rates in the following body systems:

- Infections and infestations
- Metabolism and nutrition disorders
- Musculoskeletal disorders.

The increased incidence of vascular disorders among *high risk* subjects approached, but did not reach, statistical significance. When data was combined from 851-CR1 and 851-CR3, the adverse event rate for the metabolism and nutrition disorder body system showed the only statistically significant difference: 7.1% among *high risk* subjects vs. 1.7% among *non-high risk* subjects. This difference was most likely due to preexisting diabetes and renal disorders and not related to tolerance of MiraLax therapy. Table 21 compares the

adverse event incidences for *high risk* verses *non-high risk* subjects by MedDRA Body System.

Table 21: Comparison of adverse event (AE) rates in *high risk* subjects and *non-high risk* subjects from Studies 851-CR1 and 851-CR3

Adverse Events	High Risk* (N = 99)	Non-High 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)

*The sponsor defined a high risk subject as one with a medical history significant for heart problems, kidney problems, and/or diabetes.

Overall, 71% of *high risk* subjects and 69% of *non-high risk* subjects experienced at least one adverse event during their respective studies. However, the *high risk* subjects experienced an average of 2.4 adverse events per person (with each person listed only once per body system) and *non-high risk* subjects experienced an average of 1.3 adverse events per person.

For common GI adverse events, the high risk subjects did not experience higher incidences of adverse events compared to non-high risk subjects (Table 22).

Table 22: Comparison of GI adverse event incidence for *high risk* and *non-high risk* subjects treated with MiraLax (Studies 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)

7.1.5.6.5 Effect of concomitant use of MiraLax and narrow therapeutic index (NTI) drugs on adverse events

The sponsor analyzed study subjects using MiraLax and any narrow therapeutic index drug. Forty-two subjects enrolled in Studies 851-CR1 and 851-CR3 used narrow therapeutic index (NTI) drugs while also using MiraLax. Table 23 illustrates the NTI drugs used by the subjects. During study participation, five of these 42 subjects required dose adjustment of a NTI drug.

Table 23: MiraLax subjects treated with narrow therapeutic index (NTI) drugs		
NTI Drug	**Subjects using (N = 42)**	**Subjects needing dose change**
Levothyroxine sodium	35	2
Digoxin	7	1
Warfarin	8	1
Guaifenecin	3	0
Phenytoin sodium	2	1
Carbamazapine	1	0
Lithium	1	0
Valproate semisodium	1	0

The five subjects requiring a dose change for a NTI drug are described below in Table 24:

Table 24: Study subjects using MiraLax who required dose adjustment of a concomitant narrow therapeutic index drug

Study/ patient	Age/ Gender	MiraLax Use		Medical History/Medications	Description	Related to MiraLax use?
		Start	Stop			
851-CR1: 149-019	58 F	05/05/2004	10/27/2004	Seizure disorder (Jacksonian, tonic-clionic, "shock") Depression Phenytoin 300 mg QD	Phenytoin dose was decreased to 200 mg QD in May 2004. Subject had a seizure on May 9. On June 9, a seizure resulted in loss of consciousness and head trauma. She was hospitalized and treated for seizure disorder, hypertension (HTN), depression, scalp laceration, and concussion. Phenytoin was increased and was 300 mg QD at discharge.	Unlikely Related*
851-CR3: 110-062	60 F	08/08/2003	08/09/2004	Hypothyroidism Synthroid 0.1 mg QD	Between study visits, Synthroid dose was increased to 0.125 mg QD on 01/01/2004. Dosage change was not triggered by adverse events. TSH was normal at study enrollment.	Unlikely Related*
851-CR3: 129-067	58 F	08/13/2003	08/25/2003	Hypothyroidism Synthroid 0.1 mg QD	Baseline TSH was 0.1 μU/mL, which is below the lower limits of normal. The subject was discontinued from the study, and the Synthroid dose was reportedly modified.	Unrelated
851-CR3: 129-424	68 F	10/24/2003	10/25/2004	Cerebrovascular accident in 2000. Osteoarthritis Warfarin 2.5 – 5.0 mg QD	Subject underwent a scheduled lumbar fusion on 06/01/2004. During the preoperative period, the warfarin was discontinued (05/27/04), and it was resumed at the previous dose 06/07/2004.	Unrelated
851-CR3: 135-416	65 F	10/07/2003	10/04/2004	Irregular heart beats Digoxin 0.025 mg QD	On 07/02/2004, digoxin dose was decreased to 0.0125 mg QD and verapamil hydrochloride 10 mg QD was started for the same indication. This dosing change occurred between study visits. The subject did not report any adverse events related to MiraLax use.	Unrelated

* The investigators considered these events unrelated to MiraLax use; however, this reviewer feels that without additional information and possibly a rechallenge, it is difficult to be certain that daily MiraLax use did not reduce serum levothyroxine and phenytoin levels in these subjects.

Additional comments concerning a potential effect of MiraLax use on serum levels of NTI drugs are located in Section 7.4.2.5.

7.1.6 Less Common Adverse Events

In Study 851-CR1, there were three cardiac events among subjects treated with MiraLax and none among placebo treated subjects (not a statistically significant difference). The three cardiac events included a new diagnosis of mitral valve prolapse (and associated symptomatology) in a 64 year old female Type I diabetic, one episode of supraventricular tachycardia (SVT) in a 32 year old female with a history or SVT, and an episode of tachycardia in a 70 year old female with no significant medical history. The investigators concluded that these events were not related to MiraLax treatment, and these subjects continued to use MiraLax for another three to five months.

In addition, four subjects in Study 851-CR3 experienced a cardiac related event during the study:

- A 75 tear old female subject (102-002) with a history of atrial fibrillaton, atherosclerotic cardiac disease, hypertension, chronic obstructive pulmonary disease, and hyperthyroidism reported an exacerbation of her atrial fibrillation three months after starting MiraLax treatment. Concomitant medications included multiple drugs that list atrial fibrillation as a potential adverse reaction: venlafaxine, celcoxib, levothyroxine, and diltiazem. She continued MiraLax treatment and completed the 12 month study.

- A 64 year old female subject (112-117) taking levothyroxine (Synthroid) for hypothyroidism reported an episode of cardiac arrhythmia three months after starting MiraLax treatment. One month earlier she had started venlafaxine. The subject completed the study.

- A 50 year old female subject (120-179) experienced anxiety and tachycardia after taking meclizine and venlafaxine. This occurred nine months after starting MiraLax treatment, and the subject completed the study. This subject also reported vertigo four months earlier. According to product labeling, tachycardia is listed as an adverse effect for meclizine and venlafaxine. Arrhythmia is listed as a possible adverse effect in the venlafaxine label as well.

- A 51 year old female subject (132-079) with a history of palpitations, mitral valve prolapse(MVP), hypertension, and panic disorder reported palpitations 11 months after starting MiraLax treatment. The subject was using multiple medications that list various cardiac effects as possible adverse effects: amlodipine/benazepril, hydrochlorothiazide, naproxen, and alprazolam. Alprazolam lists syncope and tachycardia as adverse reactions. This reviewer also notes that the subject's palpitations could have also been related to her MVP or a panic attack.

None of these episodes was associated with a diarrhea episode. There were no abnormal electrolyte levels reported in association with any of the cardiac events. The investigators considered these events unrelated to MiraLax treatment, and all subjects completed the study.

7.1.7 Laboratory Findings

Blood and urine samples were collected from subjects at baseline and at follow-up visits during Studies 851-CR1 and 851-CR3. Chemistry, hematology, and urinalysis data were collected. The sponsor presented baseline and follow-up mean laboratory values with standard deviations and analyzed changes from baseline. This information was provided in the report summaries. In addition, this reviewer evaluated ranges of laboratory values with particular attention paid to highest and lowest abnormal laboratory values and whether the abnormalities raised clinical concerns. Upon request, the sponsor submitted a line listing of all subjects and pertinent laboratory results and normal ranges for all instances where subjects had two consecutive abnormal results for a particular laboratory assessment.

7.1.7.1 Overview of laboratory testing in the development program

Table 25 summarizes the laboratory testing performed during the clinical safety and efficacy studies.

Table 25: Summary of laboratory assessments during clinical safety and efficacy studies

Study	Laboratory Assessments	Schedule
851-CR1	Comprehensive serum chemistries Complete blood count Urinalysis	Enrollment visit and visits at 1, 2, 3, 4, 5, and 6 months
851-CR3	Comprehensive serum chemistries Complete blood count Urinalysis	Enrollment visit and visits at 2, 4, 6, 9, and 12 months
851-ZCC	None	Not applicable

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study 851-CR1 was the only study that was randomized, double-blind, and placebo-controlled trial. Only laboratory data from this study allows a direct comparison between placebo and MiraLax treated subjects. However, enrollment criteria for Study 851-CR3 were identical to those for 851-CR1 and at times, the laboratory data results from MiraLax

treated subjects from both studies are presented separately and combined.

7.1.7.3 Standard analyses and explorations of laboratory data

This section should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the Phase 2-3 experience. The analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these do not represent real probabilities.

Laboratory data was collected in during studies 851-CR1 and 851-CR3 at the enrollment and end of study visits. The sponsor provided analyses of these data using measures of central tendency. This reviewer provides additional information based on comparisons of subjects in the placebo and MiraLax treatment groups with two or more consecutive abnormal laboratory values and evaluation of individual subjects with outlying laboratory values.

7.1.7.3.1 Analyses focused on measures of central tendency

There were no clinically significant changes in mean laboratory values during the six and twelve month study periods for Studies 851-CR1 and 851-CR3. A detailed table of laboratory results by visit and study is located at the end of this review in Appendix 10.4 under *Other Pertinent Information*. These tables include normal ranges, means, and ranges of experimental values.

No clinically significant differences were noted between the placebo and MiraLax treatment groups in Study 851-CR1. The sponsor did note the following statistically significant, but clinically insignificant differences, between placebo treated and MiraLax treated populations:

- Uric acid (all subjects) and for chloride (elderly subjects) were due to differences at baseline between treatment groups
- Platelets: clinically insignificant decrease in both treatment groups during study
- Cholesterol: difference between treatment groups (↓MiraLax, ↑Placebo).

In Study 851-CR3, the sponsor noted that all changes in mean laboratory values were small and within the normal range. None of these changes in mean values were clinically significant, although some reached statistical significance.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The majority of subjects with abnormal laboratory results during Studies 851-CR1 and 851-CR3 had abnormal laboratory assessments at baseline. Based on experimental laboratory ranges and a line listing of subjects and their laboratory results for all incidences of two consecutive abnormal laboratory values, the following trends were noted:

- The incidences of newly abnormal or increasingly abnormal laboratory values were about the same for placebo and MiraLax treated subjects for the following chemistry assessments: ALT, AST, bicarbonate, BUN, calcium, chloride, GGT, magnesium, potassium, and sodium.

- Creatinine increased from an already elevated baseline value in 1% of placebo subjects, 2.0% of MiraLax treated subjects in study 851-CR1 (6 month study duration) and in 1.6% of MiraLax treated subjects in study 851-CR3 (12 month study duration). Among individuals with normal serum creatinine at baseline, no placebo treated subjects developed elevated creatinine levels and 1.3% and 0.8% of MiraLax treated subjects in studies 851-CR1 and 851-CR3 developed elevated serum creatinine levels respectively.

Reviewer comment:

1. *The prescription label for MiraLax does not include a precaution or warning about patients with kidney disease. However, the proposed OTC label includes the following warning:* ***Do not use*** *if you have kidney disease, except under the advice and supervision of your doctor. This type of statement may be appropriate given that the clinical relevance of the creatinine data above is unclear especially if labeled duration of use is limited to seven days. This warning may be more appropriate in the* ***Ask a doctor before use*** *section and will be addressed in the labeling review in section 9.4.*

- MiraLax treated subjects appeared to have a higher incidence of high serum phosphate levels: 3% in the placebo group vs. 12% in the MiraLax treated group in 851-CR1. On examination of individual laboratory reports, the phosphate levels most often peaked during the third or fourth month of the study and then moderated, although this pattern was not completely consistent. Elevations in phosphate levels above the upper limit of normal were mild for most subjects. The highest serum phosphate level was 6.3 mg/dL (normal range = 2.7 – 4.5 mg/dL) and occurred in one MiraLax treated subject at study month two and one at study month five. Overall, newly elevated or persistently elevated serum phosphate levels occurred in 13.3% of MiraLax treated subjects in 851-CR1 and 8.4% of MiraLax treated subjects in 851-CR3 over up to six to 12 months of MiraLax treatment respectively.

- During the six month course of Study 851-CR1, 2% of placebo treated subjects and 1.5% of MiraLax treated subjects experienced a decrease in hematocrit of 2% or more. Similarly, over the 12 month course of Study 851-CR3, 2.6% of subjects

experienced a decrease in hematocrit of 2% or more.

- There were no subjects in Study 851-CR1 with platelets less than 124,000. In Study 851-CR3, there was one subject with severe thrombocytopenia (15,000) at baseline who was discontinued from the study. One subject treated with MiraLax and one treated with placebo had a significant thrombocytosis at visits 3 and 5 respectively with platelets = 846,000 and 815,000.

- White blood cell counts ranged between 2000 and 20,500. These highest and lowest values were seen in two placebo treated subjects at the fifth study visit for Study 851-CR1.

- Urine specific gravity remained within range for all subjects in Studies 851-CR1 and 851-CR3. One MiraLax treated subject experienced a sickle cell crisis during the study. While her urinalysis results demonstrate an increased (although still normal) urine specific gravity at the study visit following her crisis, there was no additional information available to know whether her specific gravity was elevated at the time she presented to the emergency room. In addition, individuals with sickle cell disease are often unable to concentrate their urine.

Additional details can be found in Table 26 on the following pages. This table presents abnormal chemistry laboratory results based on baseline values and changes from baseline during the course of the study. Subjects were included only if they experienced two consecutive abnormal laboratory values. All electrolyte and renal function tests were included as well as liver function tests and other enzymes with a highest value 2.5 times normal or higher. The data in this table support a lack of trends in laboratory data among MiraLax treated subjects except for those trends mentioned above.

In the appendices, under *Other Pertinent Information*, Appendix 10.5 contains a tabular listing of all laboratory abnormalities 2.5 times the upper or lower limit of normal in MiraLax treated subjects for studies 851-CR1, 851-CR3, and 851-ZCC. These tables were provided by the sponsor.