CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-551

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER REVIEW

NDA: 21-551/000/A2

Sponsor: Braintree Laboratories, Inc

Drug: HalfLytely® Bowel Prep — (Polyethylene Glycol 3350, sodium chloride, sodium bicarbonate, potassium chloride for oral solution and bisacodyl tablets).

Indication: Bowel Cleansing Prior to Colonoscopy

Date Document Received by CDER: November 10, 2003

PDUFA Due Date; May 10, 2004

Date of Draft: March 29, 2004

Medical Officer: Robert Prizont, MD.

I. Brief Background.

Braintree submitted NDA 21-151 on August 16, 2002 requesting possible approval of its pharmaceutical product HalfLytely® Bowel Prep — The HalfLytely Bowel Prep — is composed of two drugs: 2L solution of Polyethylene Glycol 3350 (PEG 3350), and 20 mg bisacodyl (bis) tablets (4 tablets of 5 mg). The two drugs, co-packed, will be used as a bowel cleansing system (BCS). BCS is the generic nomenclature applied to the class of drugs used for colon cleansing prior to colonoscopy or barium enemas. Braintree markets two BCS containing PEG 3350, i.e., GoLYTELY® and NuLYTELY®. GoLYTELY® and NuLYTELY®, are available as 4L PEG 3350 solutions (*the only difference between these two BCS is the lack of sodium sulfate in NuLYTELY*). The present 2L HalfLytely®,would decrease in half the PEG volume administered to patients. To support efficacy of the HalfLytely Bowel Prep —, Braintree submitted results from two Pivotal Studies (F38-13/14 and F38-20). Both studies were conducted under similar protocol design: randomized, single-blinded (*investigator*), active-active comparison, with inclusion of the marketed BCS NuLYTELY as active drug control. These studies, which enrolled 400 patients, revealed comparable efficacy (*good or excellent preparation*), between the HalfLytely Bowel Prep — and NuLYTELY.

Despite several serious adverse events (AEs), such as rectal bleeding after taking the 4 bis tablets (*Page 32, MO review, May 2003*), hypoglycemia in a 57 y old diabetic female after taking 4 bis tablets and upper gastrointestinal (UGI) bleeding in a 51 year old female (*Supporting Study F38-15, Page 36, MO review, May 2003*), the overall safety observed during studies conducted prior the initial submission of August 2002, appeared adequate. However, the mandatory safety update, received nine months after the initial submission, omitted inclusion of two deaths associated with use of the PEG-3350 BCS GoLYTELY, reported in the British Medical Journal issue of February 2003 (*Ayus JC et al. Fatal dysnatremia caused by elective colonoscopy. BMJ 326:382-384, 2003*). Furthermore, and of greater relevance for a possible approval and marketing of this presently proposed PEG-3350 product, the final draft label proposed by the sponsor, similarly omitted mention of the reported deaths, and other reported serious AEs with PEG-3350 BCS, such as upper gastrointestinal bleeding due to vomiting (*Mallory-Weiss Syndrome*), tonic-clonic seizures, and pulmonary aspiration.

In my review of May 2003, I concluded that the safety section of the proposed label was incomplete and required inclusion of the aforementioned reported serious AEs. The incompleteness of the safety section of the label led me to recommend an approvable action. Approval would follow completion of the safety section of the label with inclusion of reported deaths and serious AEs.

The Division Director informed Braintree of the approvable action and request to amend the label including the reported deaths, Mallory-Weiss Syndrome, seizures, and pulmonary aspiration on June 16, 2003.

II. Braintree Responses to Clinical Requests

Braintree submitted an overall response in a 12 page text (Pages 17-29, Vol 1) to the specific request included by this Division. The response answers the request for amendment of the PRECAUTIONS and ADVERSE REACTIONS label sections. *I will divide the questions and response to address the specific request for amendments. Hence, my outline will, in sequential order, first state the request, followed by a summary of Braintree response, followed by my comments to the sponsor's response.*

1. Request #1. The first clinical issue on label amendment relates to potential risks, including death, for use of the 2L HalfLytely (PEG-3350) in patients with end-stage renal failure. The approvable letter from the Division requested insertion in the PRECAUTIONS section of the following statement: '

   In the ADVERSE REACTIONS section, the sponsor was asked to include the following statement:

i. Braintree's Response.

Braintree claims that the requested statement in the PRECAUTIONS section is not appropriate. Braintree notes that changes in sodium concentration in patients with end stage renal failure were reported with the use of large PEG-3350 volumes (4L). According to the sponsor, neither GoLYTELY nor HalfLYTELY, induce electrolyte changes. Braintree further states that the use of HalfLytely with bis, will reduce volume intake, and, significantly reduce nausea and vomiting. Yet, Braintree appears to acknowledge that patients with renal failure may be at higher risk, because of their difficulty in adjusting to extreme and sudden changes in water loss or intake, as frequently occurs during administration of any PEG-3350 BCS. Braintree proposes the inclusion of the following cautionary statement in the PRECAUTIONS section (Page 18, Vol. 1):

> "*Patients should avoid consumption of large quantities of water during or after preparation of colonoscopy. Patients with impaired water handling (renal insufficiency or patients taking diuretics) that experience severe vomiting or nausea should be closely monitored including measurements of electrolytes*".

Braintree did not comply with the request to include in the ADVERSE REACTIONS section, deaths in patients with end stage renal failure given the 4L GoLYTELY. To justify its action, Braintree points out that four renal failure patients treated with NuLYTELY, or the HalfLYTELY bowel prep, had normal serum sodium levels after the PEG-3350 consumption. The four cases are shown in Braintree's Table 2 (Page 21, Vol 1, November 10, 2003 submission).

Table 2
Renal Failure Patients (n=4)
Serum Sodium
(Normal Range 135-145 mEq/L)

Patient #	Study	Prep	Pre	Post
5	F38-20	4L	138	136
79	F38-20	4L	141	144
152	F38-20	4L	141	142
74	F38-20	2L+Bis	140	140

Braintree asserts that PEG-3350 BCS preparation did not induce serum electrolyte abnormalities, or changes in serum osmolality in 172 "high risk" patients (78 assigned to HalfLytely). Diabetes, hypertension, heart attack, and the aforementioned patients with renal failure were included among these high

risk patients. Braintree then proceeds to comment on the possible reasons for the dysnatremia found in the two cases reported by Ayus et al in the BMJ. The authors considered the possibility that the hyponatremia recorded in one of the patients, may have been a consequence of stimulation and hypersecretion of anti-diuretic hormone (ADH), after the patient increased his water oral intake as a consequence of nausea, vomiting, diarrhea he experienced during the bowel cleansing with GoLYTELY. Braintree raises the alternative possibility that the colonoscopy itself may have caused hypersecretion of ADH (*Cohen DC et al. Hyponatremia as a complication of colonoscopy. Lancet 357:282-283, 2001*). The other patient cited in the article developed hypernatremia, not explained by the ADH mechanism. In both cases, Braintree disputes the role of the 4L Braintree PEG-3350 preparation.

ii. *Reviewer Comments*.

- The proposed PRECAUTIONS wording is acceptable as regards to the issue of renal failure. The inclusion seizures and pulmonary aspiration will be addressed in my comments to request #2 and #4.

- The requested inclusion of "*reported death in patients with end-stage renal failure during or after preparation with 4L GoLYTELY*", intends to inform physicians of the association between death in patients with end-stage renal failure, and the 4L GoLYTELY. It does not mention possible serum electrolyte disturbances that may have possibly developed during the 4L PEG preparation. Noteworthy, my second look of the lab data submitted in the original NDA 21-551 submission (August 2002), revealed elevations in serum osmolality in two patients. The elevations occurred with both, the 4L and 2L PEG preps, and were attributed by Braintree to non fasting (Page 77, Vol. 5, August 2003) . Similarly, I found increases in serum creatinine levels in patients administered the 4L and the 2L PEG preps (Pts #34 and #93 Page 286, Vol. 5, August 2003).

  I would accept the possible contribution of the colonoscopy in the development of hyponatremia. However, the hypernatremia can not be explained by colonoscopy alone. Further, the BJM article describes a 62 y patient who developed severe hyponatremia and seizures immediately after the GoLYTELY preparation, *prior* to the colonoscopy. She recovered after intravenous sodium chloride treatment. The article also mentions a third death. This was a male patient who received the PEG-3350 preparation, developed massive diarrhea, vomiting, aspiration, hypernatremia, and died of cardiopulmonary arrest. The authors could not obtain permission for a detail description of this case.

- The mechanistic reasoning of the sponsor is interesting, but as commented, does not refute the association between the

administration of the 4L PEG-3350 BCS and the fatal outcome in end-stage renal failure patients.

2. Request #2. The Division requested inclusion in the PRECAUTIONS section of the label a ' The Division also requested inclusion, in the ADVERSE REACTIONS of the label, of the following statement: *, tonic-clonic seizures*

i. Braintree Response.

To respond to this request, Braintree uses the same arguments as those used for association between PEG-3350 and end-stage renal failure. Braintree considers that the dysnatremia reported in the BMJ article, in which all patients developed grand mal seizures, was due to factors other than the 4L PEG-3350 ingestion, i.e., colonoscopy, drinking of large quantities of water, or, decrease stimuli to thirst and decrease water intake (in the case of hypernatremia). For both issues, Braintree argues that AEs associated with 4L PEG-3350 BCS, should not be included in the HalfLytely label. Hence, Braintree did not comply with the Division's request to include seizures in the label.

ii. Reviewer Comments.

- As mentioned, the three patients reported in the February 2003 BMJ, developed dysnatremia and grand mal seizures associated to the 4L GoLYTELY preparation. Indeed, grand mal seizures were the main "*clinical presentation*" that led to the finding of hyponatremia in the patient who had a complete recovery from the AE. She had a serum concentration of 138 mmol/L before the GoLYTELY preparation. After the preparation, her serum sodium decreased to 111 mmol/L.

- Since 1992, this Agency has received five reports of seizures associated to the use of PEG-3350 bowel preparations. The first AE submitted on December 1992, was reported by Mark Cleveland, presently Vice President of Braintree Labs. This was a 78 y old woman who took approximately 3.75 liters of GoLYTELY, she had copious diarrhea, and grand mal seizures hours later. At the time of the seizures, she had hyponatremia (112 mmol/L) and hypokalemia (2.9 mmol/L). Before the GoLYTELY intake, her serum sodium was 140 mmol/l. A CT of her brain was normal. She was intubated, treated with 3% saline, phenytoin, and had a complete recovery.

Noteworthy, two of the seizure AEs reported to the Agency developed after intake of less than 3 L of the PEG-3350 bowel preparation. Both of these cases occurred after intake of one glass to 8 ounces (2.4 L) of Colyte (Schwarz Pharma, Inc). Colyte has the same chemical formulation as GoLYTELY.

- Since 1992, there have been 8 reports of seizures associated with PEG-3350 buffered bowel cleansing preparations. The majority, in patients without prior medical history of seizures. Seizures developed in patients who took less than the 4L indicated in the label, and with as little as one glass of prep solution. There have been at least one more Med Watch report of seizures in a patient prepped with MiraLax (Braintree Labs). MiraLax is unbuffered PEG-3350 approved as a laxative. Braintree should be requested to comply with the inclusion of seizures in the PRECAUTIONS and ADVERSE REACTIONS sections of the HalfLytely Label.

3. Request #3. Include in the ADVERSE REACTIONS section the following statement: —

—

i. Braintree Response.

Mallory-Weiss syndrome, characterized by UGI bleeding due to severe retching and vomiting, has been associated with the use of 4L PEG-3350 in a few reported cases. Braintree notes that vomiting is decreased with the use of 2 L HalfLytely bowel prep. The sponsor cites the incidence of vomiting in the Halflytely and NuLYTELY, i.e., 2.7% with 2L HalfLytely patients versus 6.7% with NuLYTELY. Therefore, Braintree argues, that inclusion of the 4L PEG experience as AEs to the 2L HalfLytely label is "*potentially misleading*".

iii. *Reviewer Comments*.

- The claimed 6.7% incidence of vomiting in patients prepped with 4L NuLYTELY was observed only in Study 38-13/14. Study 38-20 did not reveal a significant difference between the 2L HalfLytely Bowel Prep and the 4L NuLYTELY. Further, the higher incidence in Study 38-13/14, was largely driven by Center 2. Even if we accept the claimed difference in the incidence of vomiting between the Halflytely Bowel Preparation and NuLYTELY, the difference was due to bisacodyl and not to the 2L PEG, as shown by the comparison of vomiting between

the 2L PEG, 4L PEG and bisacodyl in Braintree's Study F38-15 (*see Pages 37-38, MO review of NDA 21-551, August 2003*).

- Mallory-Weiss syndrome associated with PEG-3350 has only been reported a couple of times in the literature, and, it has been reported only with 4L PEG-3350 preparations. Braintree should be allowed to qualify this AE — . as an AE *reported with 4L PEG preps*. The AE should be kept in the HalfLytely Bowel Prep label because of the seriousness of the event, i.e., upper gastrointestinal bleeding, and because the difference in vomiting between 4L and 2L PEG-3350 solutions was not universal. Due to the infrequency of this AE, it may have not been captured in the rather small sample size enrolled in this NDA pivotal studies (<200 HalfLytely patients).

4. Request #4. Request #4 is the following: incorporate in the ADVERSE REACTIONS Section of the label, the following statement: "

i. Braintree Response.

I was unable to find a specific Braintree response addressing this request.

iv. Reviewer Comments.

- My update search of the literature resulted in the finding of more than one reported case of pulmonary aspiration. Marschall and Bartels reported three cases of pulmonary aspiration probable related to PEG solution administration. One patient, a 78 y old woman, died after developing adult respiratory distress syndrome. All three patients received the PEG solution by nasogastric (NG) tube [*Marschall HU and Bartels F. Life-threatening complications of nasogastric administration of polyethylene glycol-electrolyte solutions (GoLYTELY) for bowel cleansing. Gastrointest Endoscopy, 47:408-410, 199]*).

  In the Safety Update included in the present submission, Braintree lists two cases of pulmonary aspiration during GoLYTELY administration. In both cases, GoLYTELY was administered through an NG tube (Page 31, Vol 1, this submission).

- I would propose to move this AE to the PRECAUTIONS section. A statement in this section should —

III. Brief Summary of the Submitted Safety Update.

The sponsor submitted a Safety Update of all Braintree currently approved PEG-3350 products. These AEs were reported after the last safety update included in NDA 21-551 (submitted on 5/12/03). This present update includes 4 AEs that occurred with GoLYTELY (2 pulmonary aspirations), 4 with NuLYTELY, 8 with MiraLax, and one with an unknown PEG lavage preparation. One of the NuLYTELY cases was a 60 y old woman, who vomited blood (after intake of orange flavor NuLYTELY). She had a history of GERD and was prescribed isomeprazole. The AE reported with unknown PEG preparation was a 70 y old woman who developed hyponatremia, and was found "*in a coma with seizures*" following preparation for colonoscopy. She was admitted to the hospital with a serum sodium of 113 mmol/l. The patient recovered and is doing well. The following is the list of AE reported in this Safety Update (Page 30, Vol. 1).

	ADR#	TYPE	Submitted	Description
GoLYTELY (NDA 19-011)	030009	periodic	2003 Annual, 9/13/03	allergic reaction
	030010	periodic	2003 Annual, 9/13/03	allergic reaction
	030022	15-day	/	aspiration
	030025	15-day		aspiration
NuLYTELY (NDA 19-797)	030013	15-day	—	vomiting w/blood
	030015	periodic	2004 Annual, *pending*	vomiting
	030017	periodic	2004 Annual, *pending*	delayed action
	030024	periodic	2004 Annual, *pending*	allergic reaction
MiraLax (NDA 20-698)	030011	periodic	2003 Annual, *pending*	allergic reaction
	030012	periodic	2003 Annual, *pending*	cramping
	030014	periodic	2003 Annual, *pending*	hair loss
	030016	periodic	2003 Annual, *pending*	allergic reaction
	030019	periodic	2003 Annual, *pending*	allergic reaction
	030020	periodic	2003 Annual, *pending*	allergic reaction
	030021	15-day	—	penal bleeding
	030023	15-day	—	irritable, crying, lethargic
unknown PEG lavage (reported, NDA 19-011)	030018	15-day	—	hyponatremia

v. Reviewer Comments.

- The case of the 70 y old woman with seizures and hyponatremia after the ingestion of a PEG-3350 lavage, further emphasizes the need for inclusion of seizures in the HalfLytely label.

IV. Conclusion.

The hinge for a final approval of NDA 21-551 was the inclusion of requested safety, i.e., serious adverse events, in the PRECAUTIONS and ADVERSE REACTIONS section of the label. The requested serious adverse events were the following: #1. death in patients with end-sate renal failure given 4L — , #2. tonic-clonic seizures in patients treated with — , #3. cases of Mallory-Weiss Syndrome, upper GI bleeding, associated to the use of PEG-3350 as bowel cleansing; and #4. —

Braintree did not comply with any of the requests for inclusion in the ADVERSE REACTIONS section. The only partial comply was related to renal failure, i.e., the inclusion of wording in the PRECAUTIONS section cautioning with consumption of large quantities of water in patients with renal failure or patients taking diuretics. Overall, the principal argument provided by Braintree to justify its lack of compliance with the requests in the ADVERSE REACTIONS, was that adverse events reported with 4L GoLYTELY or NuLYTELY are not applicable to the smaller volume 2L HalfLytely. As a consequence of the large 4L PEG preparations, Braintree argues, patients have large fluid losses by vomiting, diarrhea, subsequent increased thirst and water consumption, hyponatremia, seizure, and possibly death. According to Braintree, the UGI bleeding of Mallory-Weiss syndrome associated with GoLYTELY or other PEG preparations does not apply to the 2L because vomiting is significantly decreased. Further, this reviewer was unable to find a response to the request to mention in the label a —

There is some merit in the Braintree's argument that large volumes of PEG-3350 may elicit big fluid losses and more severe pathophysiological disturbances. Hence, a class action to incorporate these serious AEs should follow this review. The facts do not completely concur with Braintree justification for the lack of compliance. The request to mention death in end-stage renal failure was qualified by including that occurred with 4L — and, of relevance, did not mention mechanisms. One of the two deaths reported in end-stage renal failure in the 2003 BMJ, developed hypernatremia, and not hyponatremia. This Agency received reports of seizure with ingestion of 3.75 L, 2.4 L and one glass of GoLYTELY or Colyte. Vomiting, although decreased in the HalfLytely patients, was not universally observed in the two pivotal trials, and, was significantly different from vomiting with NuLYTELY in only one of the two pivotal trials. In fact, in Center 1 of Study F38-13/14, one patient on the 2L developed weakness

as a consequence of vomiting, and his colonoscopy had to be cancelled (Pt #39, Page 31, Vol 5, August 2002 submission). The safety update provided in this present submission, included two cases of pulmonary aspiration after administration of GoLYTELY by NG tube. Noteworthy, one of these cases was a 79 y old woman who developed lung aspiration after administration of as little as 500 cc of GoLYTELY via NG tube.

Based on the factual evidence of literature reports, submitted data in the August 2002 submission of this NDA, and the presently submitted safety update, I conclude that there is need to inform physicians, and patients, of the potential risks of any PEG-3350 bowel cleansing system, regardless of the PEG-3350 volume administered during the bowel preparation.

V. Recommendations for Regulatory Actions.

Braintree did not provide satisfactory justification for its lack of compliance. Further, the response was incomplete. I was unable to find a response to justify Braintree's lack of compliance with the label inclusion of the complication.

I recommend maintaining the approvable action for NDA 21-551. I would further recommend reiterating to Braintree the submitted requests for inclusion in the label for the HalfLytely Bowel Cleansing System. The sponsor should be allowed the following options or alternatives to comply with the Division's requests:

1. The PRECAUTIONS section should include a caution on

2. The inclusion of a caution statement about pulmonary aspiration in the PRECAUTION section may remove the need to mention it in the ADVERSE REACTIONS section.

3. The sponsor may want to decrease the impact of the Mallory-Weiss AE by qualifying it as only report it with administration of 4L PEG-3350

The sponsor should also be informed ot

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/s/

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CLINICAL REVIEW

Center for Drug Evaluation and Research

Division of Gastrointestinal and Coagulation Drug Products

Clinical Review Cover Sheet

NDA: 21-551

Sponsor: Braintree Laboratories, Inc

Drug: Half Lytely® Bowel Prep [redacted] (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets)

Date Document Received by CDER/FDA: August 16, 2002

Date Document Assigned to Medical Officer: August 21, 2002

PDUFA Due Date. June 16, 2003

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Medical Officer: Robert Prizont, MD

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Clinical Review for NDA 21-551

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approvable. A final approval will depend upon inclusion in the label of reported serious adverse events reported with the use of PEG-3350.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for Phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

In this application. Braintree proposes review and possible approval, of its pharmaceutical product Half Lytely Bowel Prep, composed of two drugs, i.e., 2L Poly-Ethylene-Glycol-3350 (PEG-3350) and 20 mg bisacodyl (bis) tablets (4 tablets of 5 mg). The two drugs, co-packed, will be used as a bowel cleansing system. Bowel cleansing systems are a generic denomination of a class of drugs used for bowel preparation (colon cleansing) prior to colonoscopies or barium enema (X-rays). The application included 2 Pivotal and 2 supportive trials. The trials enrolled a total of 760 patients, approximately 692 patients were exposed to the drugs (*the number of patients exposed to the drugs was not provided by the sponsor. The number included here is the reviewer's estimate*).

B. Efficacy

The efficacy data of the proposed 2L PEG + 20 mg bis system were principally shown in the two Pivotal Studies, i.e. F38-13/14 and F38-20. Both studies were carried out under similar protocol design, i.e.,

randomized, single-blinded (investigator), active-active controlled (compared to the approved 4L NuLYTELY). The protocol planned for demonstration of equivalence between the 2L PEG+20 bis and 4L NuLYTELY using a 90% confidence interval. Each pivotal trial enlisted 2 centers, i.e., Center 1 and Center 2 in F38-13/14, and Center 3 and 4 in F-38-20. Enlisted centers enrolled 200 patients in each pivotal trial (total of 400 in both trials). Physicians rated the preparation according to the interference of feces for an adequate colonoscopy exam, as "excellent" (no interference), "good" (minor interference), "fair" (Interference but able to solve) and "poor" (unable to perform colonoscopy). In the subsequent analysis, the sponsor compared the proportion of "successful" (excellent+good) and "unsuccessful" (fair+poor) in patients given the 2L+bis, and patients given NuLYTELY.

Study F38-13/14 had 14 discontinued patients (11 from Center 1); 190 patients were included in the "intention-to-treat" analysis. In this study, between 42% and 45% of patients given the 2L+bis were rated as "good or excellent" preparations. This range was comparable to the 41% to 51% of patients given the 4L NuLYTELY and rated by physicians as "good or excellent". The proportion of "successful" preparations was comparable with the two preparations, ranging from 86% in the 2L+bis, to 90% in the 4L NuLYTELY.

Study F38-20 included 190 patients in the "intention-to-treat" analysis. It similarly showed a comparable rate of "successful" for the two preparations, but the proportions were lower, i.e., 79% in the 2L+bis and 77% in the 4L NuLYTELY group. This lower overall proportion of successful was due to the lower physician rating of "good" and "excellent" for the 2L+bis, i.e., 39% and 40%, as well as for Nulytely, i.e., 44% and 37%, respectively.

Equivalence between the proposed 2L+bis and the 4L NuLYTELY was not demonstrated . The statistician reviewer explained that Braintree had not estimated the "*margins*" of the 90% confidence interval, as required by the "*Guidance for Industry, E10 Choice of Control and Related Issues in Clinical Trials*". The accuracy of equivalence was further hampered by the use of a single blinding design, i.e., investigators only, in a comparison between tablets+ 2L versus 4L. The close interaction between investigators and patients introduces, potentially, doubts about the integrity of the blinding.

The pivotal design excluded assessment of the individual drug components of the HalfLytely Bowel Prep — , i.e., 2L PEG-3350 and 20 mg bis tablets. Hence, *the contributions of each HalfLytely drug component to the overall efficacy of the HalfLytely Bowel* — *was not*

elucidated. The sponsor attempted to show efficacy of the individual HalfLytely drug components in supportive Study F38-15. This attempt failed for several reasons, namely: (a) The 3-way study design *excluded* the HalfLytely Bowel — and instead, compared each HalfLytely drug component to a different bowel cleansing system (NuLYTELY); (b) the protocol prospectively planned for an enrollment of 150 patients. After enrollment of 91% to 100% of patients, Braintree (and/or the single investigator) performed an unscheduled interim analysis. The result of the interim analysis revealed no statistical differences in the proportion of successful preparations between the 2L PEG-3350, 20 mg bis, and 4L NuLYTELY. After completion of the planned study and unblinding of data, Braintree proceeded to double the enrollment (150 additional patients) under the umbrella of the same protocol. Hence, the conduct of the trial disallows the use of precise statistical comparisons; (c). Even if we overlook the inadequacy of the study conduct, the results revealed no statistical difference in the proportion of successful preparations between the 2L PEG-3350 and the 20 mg bis tablets, i.e., 73% and 64%.

Braintree performed another small (60 Patients) single-investigator supportive study comparing the 2L PEG-3350 + 20 mg bis tablets to an approved 40 tablet sodium phosphate bowel cleansing system (Visicol®, InKine). Although characterized by the sponsor as single-blinded, the extreme different physical characteristics of the preparations, in a single-investigator study, challenges the integrity of the blinding. Results were inconsistent. While the proportion of patients with successful preparations was significantly higher in the HalfLytely (+ 17%), the physician rated as excellent a higher proportion of Visicol preparations (+ 21%).

Based on the results of the pivotal studies, I conclude that the efficacy of the proposed HalfLytely Bowel Prep — is clinically comparable, but not statistically equivalent, to the approved NuLYTELY. The contribution of each drug component to the HalfLytely system is uncertain, and should not be claimed as known in the label or in promotional announcements.

C. Safety

The two pivotal trials reported a total of 27 non-serious AEs. The majority of AEs were related to gastrointestinal discomfort caused by the bowel cleansing preparations, i.e, abdominal cramping, fullness, nausea, and vomiting. Braintree's analysis of the combined data from the two studies showed a fewer proportion of HalfLytely patients complaining of cramping, fullness, and nausea. However, the analysis was based solely on observations in Study F38- 13/14, and was driven by one center (Center 2). Two of the AEs in this study should be re-adjudicated as serious. One

patient given the 4L NuLYTELY developed severe vomiting and required hospital admission for intravenous treatment with fluid, electrolytes and phenergan. Another patient, randomized to HalfLytely, developed bright red blood per rectum 4 h after administration of the 20 mg bis tablets. This AE resolved spontaneously. In Study F38-20, 6 patients experienced non-serious AEs.

Four serious AEs (classified as non-serious by the sponsor) were observed in supportive Study F38-15. A patient randomized to the 4L NuLYTELY developed UGI bleeding and was diagnosed with erosive esophagitis by endoscopy. A 51 y old woman fainted and fell after taking the 4 bis tablets. Another woman, diabetic, developed hypoglycemia (30 mg/dl) after taking the 4 bis tablets. An elderly woman, randomized to HalfLytely, developed fast heartbeats and was diagnosed with an unspecified "*cardiac arrhythmia*" prior to the colonoscopy examination.

The submitted data showed no abnormalities in serum electrolytes after administration of the bowel cleansing preparation.

The scheduled 4 month Safety Update was overdue, and submitted late in the review process (nine months after the initial submission). My review revealed that the update was incomplete, i.e., did not include two deaths associated with GoLytely reported in the February 15th issue of the BMJ, 2003. The submitted safety update included two other deaths which occurred during 2002 with Golytely (9 y male), and MiraLax (90 y female).

D. Dosing

The sponsor did not conduct dose-ranging studies, and based the selection of the 2L on information provided by physiology studies with PEG-3350 and clinical reports in the literature on the use of 2L PEG.

E. Special Populations

The sponsor included 28 patients >65 y. Though this represents a small number of patients, there appears to be no difference in efficacy in this population. Overall, this elderly population tolerated well the HalfLyetly Bowel Prep — preparation.

Both tested Braintree preparations caused a higher proportion of women complaining of abdominal discomfort .

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

PEG-3350 (Polyethylene Glycol 3350) is a large molecular polymer, soluble in water or in buffer solutions. It is essentially non-absorbed throughout the intestinal tract (it is minimally recovered in the urine, ±0.06%, of oral administration). The composition of the proposed oral PEG-3350 buffer solution is identical to the approved and marketed oral NuLYTELY (Braintree Labs). In this submission, the sponsor proposes a smaller volume of the PEG-3350 solution (2 L versus 4L of NuLYTELY). The proposed 2L PEG solution would be used in co-therapy with bisacodyl tablets. The proposed TRADE NAME, INDICATIONS AND USAGE, DOSES, REGIMENS and AGE GROUPS are the following:

TRADE NAME. **HalfLytely® Bowel Prep** —

INDICATION AND USAGE. *For bowel cleansing prior to colonoscopy.*

DOSES. The recommended *single dose contains 210 g PEG-3350 dissolved in a 2 Liter buffer solution. The PEG-buffer solution is isosmotic. The system includes 4 tablets of bisacodyl, 5 mg each.*

DOSE REGIMEN. *The **HalfLytely Bowel Prep** — is administered orally. The 4 tablets of bisacodyl are taken whole with water before administering the Half Lytely.solution. After taking the bisacodyl tablets,* the proposed label recommends to *wait for a bowel movement or a maximum of 6 h, and then, begin taking the Half Lytely solution at a rate of 240 ml every 10 minutes until the rectal effluent is clear or the 2 L are consumed.* The patient should not take solids during the drug administration and abstain taking antacids one hour before the onset of drug dosing.

AGE GROUPS. The **HalfLytely Bowel Prep** — is indicated for adults. The proposed label states that "*there is no evidence for special consideration when administered to elderly patients. Of the total number of patients in the clinical studies (186), 28 were aged 65 or older, while 9.1 percent were over 75. No overall differences in safety or effectiveness were observed*". In contrast, "*safety and effectiveness in pediatric patients has not been established*".

B. State of Armamentarium for Indication(s)

A number of oral PEG 3350 and mono-dibasic sodium phosphate salts are approved as bowel cleansing systems, under prescription or OTC, for use prior to colonoscopy or colon X-rays. The following drug products are dispensed under physician prescription. Due to salty taste of buffer solutions, all PEG products are also available in fruit and lemon flavors.

- GoLYTELY™ (Braintree Labs). PEG-3350 in a buffer solution, 236 g of powder PEG 3350 is reconstituted in 4 L of isosmotic buffer solution (22.7 g of sodium sulfate, sodium bicarbonate and chloride and app 3 g of potassium chloride). The recommended dose is 4L at a rate of 240 ml every 10 minutes; the first bowel movement should occur 1 hour after the last dose. Patients can be given the solution by nasogastric (NG) tube in patients unwilling to drink it orally. GoLYTELY was the first PEG 3350 solution approved as a bowel cleansing system prior to colonoscopy or barium enema X-ray examination. GoLYTELY was approved on July 13 1984, under NDA 19011.

- COLYTE™ (Swcharz Pharma, FDA). The second PEG 3350 solution approved on October 28, 1984, under NDA 18983. The 4 L solution has an almost identical concentration to that of GoLYTELY.

- NuLYTELY™ (Braintree Labs). Approved on April 22, 1991 (NDA 19797), it is a modified version of GoLYTELY. NuLYTELY contains a higher concentration of PEG 3350, i.e, 420 g in 4L, and the buffer solution is sodium sulfate-free.

- VISICOL™ (InKine Pharmaceuticals). Approved on September 21, 2000 (NDA 21097). An oral tablet formulation containing 2 g of sodium phosphate mono and dibasic. The approved regimen is 40 tablets, to be taken in to doses of 20 tablets (the night before the endoscopy) and 20 tablets the morning of the procedure.

The following bowel cleansing systems are marketed OTC.

- FLEET® PHOSPHO-SODA® and FLEET® PREP KITS (Fleet Co). Used for many years as a laxative, the Fleet Phospho-Soda is a liquid combination of sodium phosphate mono and dibasic. The recommended dose for bowel cleansing prior to lower GI endoscopy or colon X-ray is 45 ml (containing 30 g of sodium phosphate in a buffer solution, flavored or unflavored). Fleet Phospho Kits #1 and #2 include 45 ml PHOSPHO-SODA + 4 bisacodyl 5 mg tablets + 1 bisacodyl suppository (kit #1), or 45 ml PHOSPHO-SODA + 4 bisacodyl 4 mg tablets + 1 bag-enema (kit #2). The sole approved indication for the

FLEET PREP KITS is as bowel cleansing system in preparation for a colonoscopy, or X-rays (barium enema or IVP).

- Bisacodyl 5 mg tablets, recommended in doses of 10-25 mg is approved as an OTC laxative. It is also approved as part of bowel cleansing systems in conjunction with water enemas and laxatives. Some of the bowel cleansing systems in use are off-label combinations, e.g., magnesium citrate + bisacodyl.

C. Important Milestones in Product Development

Relevant to comprehend discussed prospective study design on the planned pivotal trials, were the Pre-NDA communications between Braintree and this Division (August 1993 October,1998, February 17, 1999, May 13, 1999, December 21, 2000). The chronology and *relevant* content of these communications is particularly germane to this review.

August 1993 meeting, the sponsor was informed that Agency Regulations (21 CFR 300.50) require that contributions from each component of a combination treatment be determined. The then Division Director (Dr. S. Fredd) suggested a factorial design to demonstrate the contribution of each ingredient of the proposed combination, using either placebo or a historical control, adding that "*the latter provides less compelling evidence of efficacy*". The Division Director suggested that the *protocol include the following treatment arms: NuLYTELY alone, bisacodyl alone, and the combination of the two*". At that meeting, Braintree *stated that a trial conducted in Australia demonstrated equivalence of the combination and the 4 L solution in achieving "excellent" preparation*. The Division Director noted that the primary endpoint might be "*excellent*" cleansing if the firm is wedded to a fixed dose comparison study with a hypothesis that the combination is equivalent to 4 L of NuLYTELY in terms of colonoscopy results. Secondary endpoints might include the incidence of adverse events, the achievement of "*good*" cleansing, and decreased fluid requirement for NuLYTELY. The Director further cautioned about the need to appropriately size the study, so to be able to demonstrate equivalence between the combination and the approved 4 L preparation. Also, *the combination ought to be statistically superior to bisacodyl..*

October 1998 meeting, the sponsor presented Protocol F38-15, a study that compared efficacy of bisacodyl 20 mg tablets versus NuLYTELY 4 L. The sponsor asked whether the study was adequate to meet the requirements for a combination drug product for the 2L+bis preparation. The division responded that "*the design of the study appears adequate to evaluate the contribution of each component to the claimed effect as*

required by 21 CFR 300.50. The adequacy of the study can only be determined following a comprehensive review of the submitted data"

February 1999 letter from the Division to Braintree. The sponsor was told that extrapolating efficacy from one product to another across clinical trials, is not an acceptable approach. We recommended a design to compare 2L-+bis, 20 mg bisacodyl (bis) alone, 2 L NuLYTELY alone, and the 4L NuLYTELY. It was noted that the study needs to be sized to demonstrate equivalence between 2L and 4L NuLYTELY and superiority of each NuLYTELY to bisacodyl 20 mg.

May 1999 letter from Braintree to the Division. In this letter, Braintree reminded the Division that Protocol 38-15 was a 3-way design "*received without comments*" or considered adequate by the Division to determine contributions of each component. Braintree noted that the new proposed 4-way study design was not only "*contradictory to the prior agreement*" but provide no further information over the previous study.

December 2000 letter from Braintree to the Division. Braintree stated that investigated the feasibility of a 4-way study design and proposed a study plan to potential investigators/gastroenterologists and to a CRO Review Board (Protocol 38-21). According to Braintree, the majority of gastroenterologists declined participation in this study, and, the CEO Review Board did not approve the protocol, citing that the 20 mg bisacodyl "*is knowingly ineffective for bowel preparation*".

D. Other Relevant Information

The combination of 20 mg bisacodyl + 2 L GoLYTELY is not approved in any country as bowel cleansing system prior to colonoscopy.

E. Important Issues with Pharmacologically Related Agents

The most important determining issue for all bowel cleansing systems is the assessment of a low risk/benefit ratio. The ideal bowel cleansing system would provide a very good-to-excellent preparation for the colonoscopic examination, with a minimum of serious safety risks. All bowel cleansing systems, including PEG buffer solutions, have been associated with occasional serious side effects. OTC PHOSPHO SODA oral formulations have *Professional Labeling* in the prescription PDR. Sodium phosphate tablets are only available under prescription and have a PRECAUTION AND WARNING sections.. The *Professional Labeling*, PRECAUTIONS AND WARNINGS *of* the sodium phosphate bowel cleansing systems include information to physicians on serious side effects, i.e., serum electrolyte depletion, QT interval prolongation, seizure

development in patients with no prior history of seizures, and the occasional occurrence of fatal outcomes due to refractory hypocalcemia and cardiac arrest. In spite of isolated cases of serious side effects, i.e., UGI bleeding due to vomiting associated to Mallory Weiss syndrome, a report of pulmonary aspiration after vomiting, and three deaths, PEG buffer solutions appears to have a lower degree of safety risks, though in fairness to the phosphate solutions, PEG buffer solutions have been available for less than 20 years and only under prescription, whereas the FLEET PHOSPHO SODA has been available OTC for over four decades..

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry. PEG is a hydrophylic, nonionic, high molecular ethylene-alcohol (glycol) polymer. [redacted] will provide the PEG material. The [redacted] will be provided by [redacted]. Bysacodyl, 5 mg/tablet, is a diphenylmethane derivative. The tablets have a Sugar-Enteric Coating composed by Eudragit L 30-55, PEG-400, talc and gelatin. Manufacturers of the bisacodyl tablet and enteric-coating will be [redacted]

Eudragit L 30-55 is not present in the OTC bisacodyl formulation.

Pharmacology. The sponsor did not performed any preclinical toxicology study with HalfLytely. The pharmacologist reviewer (Tamal Chakraborti, Ph.D) states that bisacodyl is approved as a Category I OTC laxative at a dose of 5 to 15 mg/day. He also stated that the proposed 20 mg dose is approved under 21 CFR 334.66(d)(3)(iii)(a).

Statistics. Three issues have statistical relevance: *(a) doubts about the blinding integrity.* Blinding of investigators only (*single-blinding*) raises the possibility of communication between unblinded patients and investigators, casting concerns on minimization of bias, *(b) lack of appropriate design to determine the contribution of bisacodyl on efficacy.* Demonstration of bisacodyl contribution to the bowel cleansing system would have required a trial design with 4 treatments, i.e. 4L PEG versus 2L PEG versus 20 mg bisacodyl versus 2L PEG + 20 mg bisacodyl, *(c) lack of knowledge on a placebo contribution.* An argument could be made that a large liquid volume, i.e., 2 L of water or buffer taken as 240 ml (1 full cup) every 10 minutes, may have a contribution, even if small, in eliciting intestinal peristalsis and stool evacuations

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There was no submission of pharmacokinetic (PK) data for HalfLytely. For the bisacodyl, published data on 12 human subjects who received 10 mg orally in an aqueous acid solution or in an enteric coated bisacodyl tablet, revealed a Cmax of 26 ng/ml at 8 h (*Drug Research 38:570-574,1988*). Systemic bioavailability with enteric tablets ranged from 16 to 21% based upon AUC and urinary excretion. The enteric coating was not specified in the pharmacology review. As stated, the Braintree bisacodyl uses Eudragit 33-50 as enteric coating. Eudragit 33-50 dissolves at pH 7 or higher.

B. Pharmacodynamics

PEG 3350 exerts its action by osmotic pressure. Early small intestinal perfusion studies with high molecular PEG showed a net influx of water and electrolytes towards the intestinal lumen (positive flux). The buffer solution attempts to minimize the flux of electrolytes. The osmotic influx of large volumes of water caused by the hypertonic PEG induces intestinal peristalsis and watery diarrhea. Bisacodyl [4,4'-2-pyridylmethylene) bisphenoldiacetate] is an inactive pro-drug that is hydrolyzed by the intestinal brush border enzymes and colonic bacteria to bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) which is the active species. BHPM stimulates sensory nerve endings within the colon mucosa thus producing increased propulsive peristaltic contractions, which accelerate movement of contents through the colon. The action of BHPM begins about 6 to 8 hours after the bisacodyl ingestion.

IV. Description of Clinical Data and Sources

A. Overall Data

The data supporting the claim of safety and effectiveness of the **Half Lytely Bowel Prep** — were obtained from pivotal trials and supporting studies conducted by Braintree Labs. In addition, the sponsor submitted literature which may support the effectiveness of the combination of 2L PEG and bisacodyl, as well as literature on the safety effectiveness of the components.

B. Tables Listing the Clinical Trials

The application included two pivotal trials (F38-13/14 and F38-20) and two supporting studies (F38-15 and F-38-23). The trials enrolled a total of 760 patients. Table A (Page 1, Vol. 5) lists the studies, sex and mean age.

A. Table of All Studies

Study	Investigator	State	Study Preps	# pts	Sex	Mean Age	Report Volume	Data Volume
F38-13/14	DiPalma	AL MN	2L+bis 4L	200	95F 105M	58.4	1.4.2	1.4.5 A
F38-15	DiPalma	AL	2L bis 4L	300	153F 147M	54.1	1.4.3	1.4.5 B
F38-20	Bradv	TX MA	2L+bis 4L	200	84F 116M	56.3	1.4.2	1.4.5 C
F38-23	Brady	TX	2L+bis Visicol	60	32F 28M	53.0	1.4.3	1.4.5 D

4L = NuLYTELY, 4L dose; 2L = NuLYTELY, 2L dose; bis = 20 mg bisacodyl
2L+bis = NuLYTELY, 2L dose with 20 mg bisacodyl.

C. Postmarketing Experience

The **HalfLytely Bowel Prep** is not approved in any country, so there is no post-marketing experience (*other than studies reported in the literature*). There is post marketing experience with the single product components of the bowel prep system.

Since its initial marketing in 1984 to the time of this submission Braintree reports that doses of GoLYTELY have been distributed. The sponsor notes that during that period of time, there were 82 adverse events (AEs) reported . Since its approval in 1991, about doses have been dispensed, with 42 adverse events reported. According to the sponsor, the majority of these AE reports involved allergic reactions (presumably to PEG) and GI symptoms (nausea, vomiting).

The sponsor reports that in 2001 alone, it was estimated that units of bisacodyl were dispensed, either as a laxative, or as part of kits with enemas or purgatives for endoscopy or X-ray examination. There were 18 spontaneous AEs reported in the 2000-2001 period.

i. Reviewer Comments.

The postmarketing report is incomplete and needs update. Though it is true that the majority of reports included nausea, and vomiting, it is also true that in some cases, vomiting led to either a tear of small vessels in the upper region of the gastric mucosa and upper GI bleeding (Mallory Weiss Syndrome) or pulmonary

aspirations, both very serious AEs. Further, very recently a publication in a British Medical Journal, reported three deaths in patients administered GoLYTELY. These fatal outcomes occurred in the USA.

D. Literature Review

In the 1960's and 1970's, Fordtran et al used high molecular PEGs (>1000) as non-absorbable markers to conduct perfusion studies of the small intestine (transport flux of sugars, water, electrolytes). With the advent of fiberoptic colonoscopies, the non-absorbable property of the PEG polymer was investigated as a cleansing bowel system. Since the approval of GoLYTELY in 1984, and subsequent approval of COLYTE, NuLYTELY, OCL, 4L PEG-3350 or PEG-4000 buffer solutions have been used preferentially by gastroenterologists, radiologists, and surgeons as bowel cleansing systems. Though uncommon, adverse experiences have been reported, including the recent report of two deaths in patients with end-stage renal disease. The following short reference list highlights relevant literature related to high molecular PEG solutions.

1. *Fordtran JS et al. Ionic constituents and osmolality of gastric and small intestinal fluids after eating. Am J Dig Dis. 11:503-511, 1966.*

2. *Fordtran JS et al. Stimulation of active and passive sodium absorption by sugars in the human intestine. J Clin Invest, 55:531-539, 1975.*

3. *Davis GR et al. Development of a lavage-solution associated with minimal water and electrolyte absorption or secretion. Gastroenterol, 78:991995, 1980.*

4. *Goldman J et al. Evaluation of rapid colonoscopy preparation using a new gut lavage. Gastrointest Endosc, 78:9-11, 1982.*

5. *Thomas G et al. Patient acceptance and effectiveness of a balanced lavage solution (Golytely) versus the standard preparation for colonoscopy. Gastroenterol, 82:435-437, 1982.*

6. *Adler et al. Whole gut lavage for colonoscopy-----a comparison between two solution. Gastrointest Endosc, 30:65-67, 1984.*

7. *DiPalma JA et al. Colon cleansing---acceptance by older patients. Am J Gastroenterol, 81:652-655, 1986.*

8. *Sogge MR et al. Mallory-Weiss syndrome induced by the oral-electrolyte overload technique for colonoscopy preparation. Gastrointest Endosc, 26:51-52, 1980.*

9. *Paap CM et al. Acute pulmonary edema after polyethylene glycol intestinal lavage in a child. Ann Pharmacother, 27:1044-1047, 1993.*

10. *Ayus JC et al. Fatal dysnatremia caused by elective colonoscopy. BMJ, 326:382-384, 2003.*

V. Clinical Review Methods

A. How the Review was Conducted

My review was concentrated on Pivotal Studies F38-13/14 and F38-20. Supportive Study F38-15 was carefully examined, for this study was conducted by the sponsor to show the efficacy of each HalfLytely Bowel Prep — drug component, i.e., bisacodyl and PEG-3350. Small study F38-23 was reviewed and briefly mentioned, but, its results had no impact on my final recommendations

B. Overview of Materials Consulted in Review

Volumes 1.1, 1.4, 1.5 , 1.6, 1.8, and 1.12 were carefully examined. These volumes included information on pivotal study protocols, efficacy results, safety, patient tabulation, reason for discontinuations or patient exclusions, and case report forms (CRFs).

IND 28,741 (Vol. 3.1) was reviewed to assess interim analysis in Study F38-15. Action Packages on GoLytely and NuLytely were consulted to assess MO reviews and communications.

PDRs for prescription drugs and OTC were consulted to examine approved labels for GoLytely, NuLytely and Bisacodyl

Pharmacology, biopharmacology, chemistry , and particularly, the statistical review, were evaluated and relevant parts and information incorporated in various sections of this review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

— No information has been received on DSI inspections. According to information provided by this Division PM in charge, inspections will not be conducted, according to regulations on co-package drug combination.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

My review of patient consent forms, IRB letters, and data from CRFs, indicate that patient rights were protected according to the World Medical Association Agreement of Helsinki.

E. Evaluation of Financial Disclosure

In APPENDIX 1 of the November 25, 2002 submission, Braintree included FDA Form 3454 for investigators — — Braintree certifies in this signed form, that it did not enter into any financial agreement with these investigators.

In the same submission and in a separate signed FDA Form 3455, as concerned to investigator — , and for Studies — Braintree checked a section, it amended it, and stated that it did not incur in "any significant payments of other sorts for the duration of the clinical trial 1993-1998" from the sponsor of the covered study.....or honoraria. In an Attachment (to Form 3455), Braintree proceeded to list honoraria paid to — , from — (51,800$). Braintree noted that the studies were — , "Study — , and "*value of compensation was not affected by the outcome of any study*".

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Based on the data from pivotal and supporting trials, the sponsor concludes that "*Braintree Laboratories has demonstrated in well-controlled, adequately powered clinical studies that 2L+bis is an effective, well-tolerated regimen for bowel cleansing. It is equivalent in efficacy to 4L of PEG-ELS, yet superior in patient acceptability and side effects, probably due to its reduced volume*" (Page 49, Vol. 1).

This reviewer's conclusions will be discussed after the presentation of the clinical trials. Briefly, the submitted clinical trials show efficacy with the HalfLytely Bowel Cleansing Prep. Unlike what is claimed by Braintree, the HalfLytely Bowel Cleansing Prep efficacy does not meet the needed requirements to be qualified as statistically equivalent, though, it may be clinically comparable to the approved NuLYTELY.

B. General Approach to Review of the Efficacy of the Drug

Braintree conducted four clinical trials. The four clinical trials, investigators, number of subjects enrolled, proportion of sex and mean average was listed in Braintree's A. Table of All Studies, included in a previous section of this review (*Section IV. Description of Clinical Data and Sources. Subsection B. Tables Listing the Clinical Trials*). My review will concentrate in more detail on the trials designated by Braintree as Pivotal Clinical Trials, i.e., F38-13/14 and F38-20. I will briefly describe and comment supporting trials F38-15 and F38-23.

C. Detailed Review of Trials by Indication

- *Note from the Reviewer. My review of efficacy will be first directed to the two Pivotal trials. I will provide a brief summary of the relevant sections of the protocol. Subsequently, I will proceed to describe the results. After description of efficacy data from both Pivotal trials, I will include a section with my comments (Reviewer Comments). Each supportive trial will be described and followed by reviewer comments*

I. Pivotal Clinical Trials.

1. Study F38/13-14.

The prospective Protocol for Study F36/13-14 was Protocol F38-10 (Page 81,109, Vol. 5, or Braintree's Vol. 1.5), submitted on June 1993 under IND 28,741. *The following are the relevant sections of the protocol.*

(a) Design and Sample Size. Randomized, single blinded (investigators) with a planned enrollment of 200 .

(b) Inclusion Criteria.

- Subjects who are 18 years or older who will be undergoing a colonoscopy "*for routinely accepted indications and are not pregnant or lactating*".

(c) Exclusion Criteria (adequate for the purpose of the study; included in the Patient Selection section of the protocol).

- ileus
- possible intestinal obstruction or perforation
- prior GI surgery

- gastroparesis or gastric outlet obstruction
- impaired consciousness that predisposes to pulmonary aspiration.

(d) Drugs. The test drug: 5mg bisacodyl tablets followed by 2L NuLYTELY. Control drug: 4L NuLYTELY.

(e). Efficacy Endpoint (scanned from the study protocol, page 21).

Score	Grade	Description
1	poor	large amounts of fecal residue, additional cleansing required
2	fair	enough feces or fluid to prevent a completely reliable exam
3	good	small amounts of feces or fluid not interfering with exam
4	excellent	no more than small bits of adherent feces/fluid

Grades 3 - 4 are considered successful; grades 1 - 2 unsuccessful. Each examination will also be rated simply as clinically acceptable or unacceptable.

The protocol planned (Page 15) for a calculation of the observed delta between ratings successful (excellent + good) and unsuccessful (fair + poor).. The "*90% confidence interval for the observed delta for this difference in proportion of successes will be calculated. The criteria for equivalence between groups on the primary variable of the proportion of successful preparations observed will be (a) a non-significant test of equality ($p<0.05$) and, (b) the delta for the difference in proportion of successful preps falls within the calculated 90% confidence interval*".

1.f. Results (Vol. 1.5, Pages 20-29).

- *Demographic Data.*

Braintree randomized 200 consecutive patients in two medical centers Center 1 = Mobile, AL, and Center 2 = Rochester MN. The overall demographics of the 200 randomized patients has already been shown in the aforementioned A. Table of All Studies. In the next Braintree Table 4, the sponsor included the demographics for each center. As noted, there were more males and African Americans enrolled in

Mobile, while there were more females and only Caucasians enrolled in Rochester (MN).There was a significant difference in age between the centers, i.e., population was 6 years older in Rochester ($p<0.01$). Uncertain is whether these demographic differences may have altered (or not) the efficacy results.

Table 4
Demographic Data
(Braintree Protocol F38-13/14)

Center	Mean Age	Mean Weight	Male	Female	Race AA	Race C
1 (Mobile)	54.8	180.5	46	54	23	77
2 (Rochester)	61.9	180.2	59	41	0	100
Totals	58.4	180.4	105	95	23	177

AA = African American, C = Caucasian

Efficacy

The sponsor reports that 14 subjects did not complete the protocol. Three patients were excluded for non-compliance with the protocol (40, 55, 92, all from Center 1); 7 withdrew for "personal reasons" (16, 24, 30, 44, 66 from Center 1, and 103, 183), 4 were unable to complete the protocol due to an unexpected AE (19, 26, 39 from Center 1)

Braintree excluded from the primary efficacy analysis the 14 patients who " did not complete the protocol". Hence, 186 patients were included in the efficacy analysis of patients who completed the protocol. In the next Table 5 , Braintree shows the proportion of excellent, good, fair, poor in the two treatment groups. Physicians rated the colon preparation in a 4 rating scale, ranging from 1 (poor) to 4 (excellent). Braintree notes that there

Table 5
Physician Rating of Preparation
(Braintree Protocol F38-13/14)

Rating	4L NuLYTELY	2L+bis
4 (excellent)	51.6% (48)	45.2% (42)
3 (good)	40.9% (38)	41.9% (39)
2 (fair)	5.4% (5)	10.8% (10)
1 (poor)	2.1% (2)	2.2% (2)
Mean Rating	3.4	3.3
Mean Ridit	0.5	0.542
SE	-	0.030
z	-	1.4
p	-	0.16

were no significant statistical differences between the groups.
In Table 6, Braintree depicts the proportion of "*successful*" preparations (excellent + good) versus failures or "*unsuccessful*" preparations (fair + poor) in the two treatment groups. In this Braintree's "intention-to-treat" analysis, there were 190 patients included. The four additional patients included had discontinued the trial because of AEs occurring prior to complete their preparations.

Table 6
Bowel Preparation Success
Intent-to Treat
(Braintree Protocol F38-13/14)

Rating	4L NuLYTELY	2L+bis
Successful	89.6% (86)	86.2% (81)
Unsuccessful	10.4% (10)	13.8% (13)

X2 = 0.52, p = 0.47
90% CI = 89.6% ± 7.2%

Braintree states that Table 6 shows that there were no statistically differences between preparations in the proportion of "successful" and "unsuccessful". Braintree notes that *100% (92 patients) of the completed 4L preparations were rated as clinically "adequate". Instead, 6 of 93 (6.5%) of the 2L preparations were rated as clinically "inadequate". This difference was significant (p<0.05). Ratings were unrelated to sex, age or race (underlying by this reviewer).*

The subset comparison of all completed preparations in the 2 Centers, revealed a significant difference (p=0.05) between them, in the proportion of "*unsuccessful*" preparations, i.e., 17% in Center 1, Mobile (16 of 92) versus 7% in Center 2, Rochester (7 of 98).

2. Study F38-20.

The study protocol for this pivotal study is basically identical to the protocol described for the previous study. The terms acceptable or unacceptable preparation described in the primary endpoint of the previous protocol were replaced by adequate or inadequate.

2.f. Results (Vol. 1.5 Pages 235-239)

- *Demographic Data*

The two enlisted centers, i.e., Center 3, (San Antonio, TX), and Center 4 (Braintree, MA), enrolled a total of 200 consecutive patients. Center 3 enrolled 75% of the patient population (150), and Center 4 enrolled 25% (50). With the exception of the large proportion of Hispanics and African Americans enrolled in Center 3, there were no differences in proportion of males/females or in average patient age. The demographic data are illustrated in the next Braintree Table 4.

Table 4
Demographic Data
Protocol F38-20

Center	Mean Age	Mean Weight	Male	Female	Race AA	C	H
3 (SA)	56.7	191.3	85	65	23	60	67
4 (Braintree)	55.1	188.9	31	19	2	47	0
Totals	56.3	190.7	116	84	25	107	67

AA = African American, C = Caucasian, H = Hispanic
Note: one patient in Center 4 refused to identify race.

- *Efficacy*

The initial efficacy analysis was based on 188 patients who completed the protocol. Braintree reports that 12 patients did not complete the protocol (Center3=10, Center 4=2). Five patients were excluded prior to administering the preparation for non-compliance with the protocol; five patients withdrew due to illness prior to preparation and two patients were unable to complete the preparation due to an AE (nausea or vomiting). Physician ratings of excellent, good, fair, poor, of the 188 patients who completed the preparation is shown in the next Braintree Table 5.

Table 5
Physician Rating of Preparation
(Braintree Protocol F38-20)

Rating	4L NuLYTELY	2L+bis
Excellent	36.5% (35)	40.2% (37)
Good	43.7% (42)	39.1% (36)
Fair	18.8% (18)	18.5% (17)
Poor	1.0% (1)	2.2% (2)

$\chi^2 = 0.79$, $p = 0.85$

As in the previous pivotal study, Braintree 's intention-to-treat analysis was based on 190 patients. In this study, the two additional patients were patients unable to complete the preparation because of an "expected" AE and did not undergo endoscopy (both had been assigned the 4L). The comparison between drugs is illustrated in the next Braintree Table 6.

Table 6
Bowel Preparation Success
Intent-to Treat
(Braintree Protocol F38-20)

Rating	4L NuLYTELY	2L+bis
Successful	76.8% (77)	79.3% (73)
Unsuccessful	21.4% (21)	20.7% (19)

$\chi^2 = 0.02$, $p = 0.9$
90% CI = 76.8% $\pm$ 6.8%

As stated by the sponsor in the submitted report, this table shows that there was no statistically significant difference between the preparations with respect to "*successful*" (excellent+good) and "*unsuccessful*" scores.

i. Reviewer Comments.

ii. *The efficacy results from the two pivotal trials achieved, in considerable degree, the goal stated in the study protocols, that is, to show "comparability" between the proposed 20 bis + 2L Nulytely*

and the approved NuLYTELY 4L PEG-3350 bowel cleansing buffer solution. Hence, the submitted data from both pivotal trials show the proportion of patients (Braintree's intent-to-treat) with "successful" preparations, >85% to be comparable with bowel cleansing systems. The "success" rate increases to >90% if we only include patients who completed the protocol (per-protocol analysis). The use of the term "comparability" (and not equivalence) seems appropriate in this case, for the design of the study did not comply with the requirements stipulated in the Agency's "Guidance for Industry, E10 Choice of Control Group and Related Issues in Clinical Trials". As explained by the reviewer statistician, the guidance establishes that in order to demonstrate equivalence (or non-inferiority) the sponsor should have prospectively calculated that the new drug is not less effective than the approved NuLYTELY. by a pre-determined "margin" or amount.

iii. *The "equivalence" terminology is further challenged because the design of the trials did not fully comply with adequacy of well-controlled trials, in accordance of CFR 21 314.126, i.e., use of procedures that will minimize bias. The study protocol used for these pivotal trials stated that only investigators will be blinded. Patients from a center were randomized to one of the two treatments and had to be informed that they may be assigned (randomized) to two different preparations, i.e., one treatment included 4 tablets whereas the other treatment did not . The ensuing potential for unblinding investigators was almost on the surface given the known close interactions between physicians (investigators) and their patients. As a consequence, these were randomized but, at least potentially, open-label trials. The statistician reviewer (Dr. W Chen) tested the robustness of the result by performing a sensitivity analysis. Dr. W Chen applied, as a margin, the 16% success <u>difference</u> between NuLyTELY and 2L + bis used by Braintree to calculate sample size. It should be noted that a difference in success to calculate sample size, is <u>not</u> a <u>margin</u> of a confidence interval, but, an estimate of efficacy <u>superiority</u>. The sensitivity analysis would test whether the <u>lower limit</u> of the 90% confidence interval does not fall below the 16%. If the efficacy results were robust, the lower limit of the confidence interval would not be altered by just 2 changes, e.g., from fail to success of 1 patient in the NuLYTELY group, plus, a reverse change from success to fail in 1 single patient of the 2L+bis group. Yet, these 2 changes resulted in a -17% lower limit unfavorable to 2L+bis, i.e., below the -16% lower boundary used by Braintree.*

iv. *The proposed HalfLytely Bowel Cleansing — is composed of two active drugs, i.e., 2L Nulytely, and, 20 mg bisacodyl. Bisacodyl is an active drug approved for use as part of bowel cleansing systems. The knowledge of the contribution of each drug component, 2L PEG-3350 and 20 mg bisacodyl, is of relevance for compliance with regulatory requirements,. Regulations, i.e., CFR 21 300.50, require to determine the contribution of each drug component to the to overall the drug combination. Further, information on the efficacy of each drug component is important for a better understanding of the clinical effectiveness of the drug combination. The lack of inclusion in the pivotal studies of each drug component, 2L PEG-3350 and 20 mg bis, precludes full compliance with the regulations and understanding of the contribution by each individual drug to the combined drug efficacy. Yet, 2L PEG-3350 and 20 mg bisacodyl may be considered co-therapies, in which case the combination rule may not apply.*

v. *In trial F38-13/14, there was an apparent imbalance in the number of patients discontinued in Center 1, i.e., 11, and, Center 2 , i.e., 3. This imbalance was statistically significant ($p<0.01$). The apparent imbalance in discontinued patients did not impact on the efficacy results, for the number of patients discontinued in both treatment arms was the same (2l+bis=7, 4L PEG-3350=7). The high rate in discontinued patients explains, in part. the higher proportion of unsuccessful preparations observed in Center 1.*

II. Supporting Studies

3. Study F38-15

According to the sponsor, this 3-treatment arm study was designed to determine the efficacy of each of the ***HalfLytely Bowel Prep*** — drug components, i.e.20 mg bisacody, 2L NuLytely. The third treatment arm was the 4L NuLYTELY. Inclusion and exclusion criteria, efficacy endpoints of the study protocol study were identical to similar sections included in the protocol for pivotal trials. The original protocol, submitted to this Division on June 6, 1993 under IND 28,741 planned for an enrollment of 150 consecutive patients in a single center (Mobile, AL).

The study began in 1993 and after completion of 137 patients, Braintree performed an "interim analysis". The efficacy results, i.e., fail or success, did not reveal significant differences between bisacodyl, 2L Nulytely, and 4L NuLYTELY. The next Table (Page 50, Vol 1.5) illustrate the results.

Investigator Examination Rating
Braintree Protocol F38-15
Interim Analysis

Rating	Bisacodyl (n=45)	2L (n=45)	4L (n=47)
Fail	19 (42.2%)	11 (24.4%)	10 (21.3%)
Success	26 (57.8%)	34 (75.6%)	37 (78.7%)

$X^2 = 5.61$, $p = 0.06$

Subsequent to examination of the efficacy data, Braintree submitted *"a revised protocol"* to the Division, expanding the enrollment to 300 patients. The remaining 163 patient were enrolled in the single center enlisted for the trial (Mobile). Of the 300 enrolled patients, 264 completed the trial. The following Braintree Table 1 (Page 7, Vol. 6) illustrates physician efficacy ratings of excellent, good, fair, poor, of the 264 patients who completed the trial..

Table 1
Physician Rating of Preparation
(Braintree Protocol F38-15)

Rating (score)	Bisacodyl % (n)	2L Prep % (n)	4L Prep % (n)
Excellent (4)	19.5 (17)	17.6 (15)	41.1 (38)
Good (3)	44.8 (39)	55.3 (47)	42.4 (39)
Fair (2)	18.4 (16)	12.9 (11)	8.7 (8)
Poor (1)	17.2 (15)	14.1 (12)	7.6 (7)
Ave Score	2.7	2.8	3.2

Brainttree states that the patient group comparison of the different ratings, e.g., excellent revealed significant superiority of the 4L over the 2L, and over bisacodyl 20 mg ($p<0.001$).

In the next Braintree Tables 6 shows physician ratings of the proportion of patients in each drug-group with *successful* (excellent + good) and *unsuccessful* (fair + poor) preparations NuLYTELY 4L was significantly different from bisacodyl, but not different from the 2L Nulytely.

Table 6
Bowel Preparation Success
(Braintree Protocol F38-15)

Rating (score)	Bisacodyl % (n)	2L Prep % (n)	4L Prep % (n)
Successful (score = 3+4)	64.4% (56)	72.9% (62)	83.7 (77)
Unsuccessful (score = 1+2)	35.6% (31)	27.1% (23)	16.3 (15)

X^2 overall = 8.71, p = 0.01
X^2 bis vs 4L = 8.75, p =0.003
X^2 2L vs 4L = 3.03, p = 0.08

The data in the next Braintree Table 7 (last submitted table on efficacy) compare the proportion of patients rated by physicians as having adequate or inadequate preparations. The comparison revealed no statistically significant difference between the 4L, 2L, and bisacodyl.

Table 7
Physician Rating of Clinical Adequacy
(Braintree Protocol F38-15)

Rating (score)	Bisacodyl % (n)	2L Prep % (n)	4L Prep % (n)
Adequate (1)	80.5 (70)	83.3 (70)	92.3 (84)
Inadequate (2)	19.5 (17)	16.7 (14)	7.7 (7)

X^2 overall = 5.50, p = 0.06

i. Reviewer Comments.

vi. *The relevance of the efficacy data provided in this supportive study is limited, for instead of comparing the individual drug components of the proposed HalfLytely Bowel Cleansing System to the HalfLytely Bowel Cleansing — it compared them to NuLYTELY. Hence, the absence of HalfLytely Bowel Cleansing — prevents to provide the relevant data, the degree of*

efficacy contributions of each drug component, i.e., 2L Nulytely and 20 mg bis, in the efficacy of the proposed drug combination. Noteworthy, the efficacy data of this study revealed that the 20 mg bisacodyl is not significantly inferior to the 2L NuLytely. In fact, proportion of excellent preparations rated by the physician was similar in the 20 mg bis and 2L Nulytely (see Braintree's Table1). This observation was further confirmed by the physician/investigator, who rated 81% of the 20 mg bis preparations as "clinically adequate", similar to the 83% rating who gave to the 2L Nulytely preparations.

vii. *The adequacy of this study, and hence the validity of its results, are unconvincing. My conclusion is based on two observations: (a) lack of blinding of the bis tablets and the 2L Nulytely with a double-dummy placebo, (b) the conduct of the study. For, the conduct of a clinical study is seriously damaged when failed efficacy results revealed in an announced unblinded interim analysis, performed after completion of 91% of planned patient enrollment, leads to a subsequent continuous enrollment with the aim to double the sample size and achieve successful results.*

4. Study F38-23

This open-label, single center (San Antonio, TX), compared the efficacy of the HalfLytely Bowel Prep — to Visicol® (sodium phosphate) 2 g tablets.(1.1 g sodium phosphate). Visicol® (InKine Co) tablets are approved as a cleansing bowel system prior to colonoscopy. The study enrolled 60 consecutive patients (*28M/32F, 55% Hispanics, 33% Caucasians, 12% African American*); 54 completed the protocol. The protocol was similar to the study protocol used for the pivotal studies.

The next Tables 5 and 6 (*scanned* from Pages 148-149, Vol. 6) exhibit comparison of efficacy. The drug comparison of physician ratings by the 4 categories of excellent, good, fair, and poor, revealed no statistical difference between preparations (Table 5). The drug comparison in the *successful* (excellent + good) and *unsuccessful* (fair + poor) revealed statistical significance favorable to the HalfLytely bowel system (Table 6).

Table 5
Physician Rating of Preparation
(Braintree Protocol F38-20)

Rating	Visicol	2L+bis
Excellent	42.3% (11)	21.4% (6)
Good	46.2% (12)	75.0% (21)
Fair	11.5% (3)	3.6% (1)
Poor	0% (0)	0% (0)

$\chi^2 = 4.86$, $p = 0.09$

Reviewer's Note. The table states, erroneously, that data are from "Protocol F38-20".

Table 6
Bowel Preparation Success
Intent-to-Treat
(Braintree Protocol F38-23)

Rating	Visicol	2L+bis
Successful	79.3% (23)	96.4% (27)
Unsuccessful	20.7% (6)	3.6% (1)

(n) = number of patients
$\chi^2 = 3.88$, p = 0.05; 90% CI = 79.3% ± 5.8%

i. Reviewer Comments.

viii. *The rationale to perform this open-label, small patient population study, between the approved Visicol® tablets is unclear. Further, the comparison rendered contradictory results. While the overall rating of successful (excellent + good) was statistically superior to the Halflitely Bowel the physician rated as "excellent" preparation a clinically significantly higher proportion of patients administered Visicol than on the HlafLytely, i.e., 41% versus 21%, respectively.*

D. Efficacy Conclusions

The efficacy of pivotal and supportive trials shows that the ***HalfLytely Bowel Prep*** *is clinically comparable to the 4L NuLYTELY.*

The design of the pivotal studies did not allow demonstration of equivalence between bowel cleansing systems. The contributions to the overall efficacy of each drug component was not elucidated for, the conduct of supportive trial F37-15, that tested the drug components, was inadequate, and hence, the validity of its results, are in doubt. If I would consider the results of this supportive F38-15 study as acceptable, I would then conclude that the 20 mg bis tablets and the 2 L NuLytely exhibit comparable bowel cleansing efficacy and contribute equally to the overall co-therapy of HalfLytely..

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Overall, there were no serious AEs reported in patients administered HalfLytely Bowel — , i.e., deaths, tonic or tonic-clonic seizures, acute cardiac events such as arrhythmias due to electrolyte imbalances Prep or the 4L NuLYETLY in the two Pivotal trials (F38-13/14 and F38-20) or Supportive trials. (F38-15 and F38-23). One patient (on 4L) required hospital admission because of severe vomiting, and one patient developed rectal bleeding (4h after bisacodyl); both recovered. One patient enrolled in supportive trial F38-15 vomited blood; endoscopy revealed esophagitis and the vomiting stopped spontaneously. The majority of AEs were "expected" AEs seen with bowel cleansing system, such as nausea, vomiting, abdominal fullness, and abdominal cramping.

Based on the reported findings, I conclude that the trials included in this NDA showed an acceptable safety margin for the proposed HalfLyely Bowel — Prep. However, as detailed in administration of approved PEG-3350 bowel cleansing products, i.e., Golytely, to renal failure patients, led to death. As will be noted, other serious AEs have occurred with the approved PEG-3350 Golytely and Nulytely. The final label should inform physicians of all serious AEs with PEG-3350 containing products

B. Description of Patient Exposure

- The sponsor did not provide a drug amount analysis of patient exposure to HalfLytely Bowel Cleansing Prep, or, to each drug component of the co-pack. A comment (1/2 page) on drug exposure was included on Page 38 of the Integrated Summary of Safety (ISS). It states that the exposure to the 2L + bis bowel preparation system consists of a "*single encounter over a brief (4 to 6 hours) period of time*". It also states that NuLYTELY has already been approved under NDA 19-797. At the request of the Division, Braintree submitted on June 4, 2003, a tabular list of the number of patients exposed to the drug, and the proportion (app >80%) who completed the protocol and were exposed to the complete doses of the Halflyte Bowel Prep
  — No data of doses/patient were included in the table.

C. Methods and Specific Findings of Safety Review

The sponsor did not design or conducted a specific study to assess safety of the ***HalfLytely Bowel Cleansing*** — . The safety data

reported are in its majority, form the two Pivotal Studies conducted (400 patients enrolled).

1. Adverse Experiences (AEs). Three hundred seventy four patients were treated with either the PEG 2L + bis or NuLYTELY in the two Pivotal Trials (F38-13/14 and F38-20). A total of 6% (24/374) AEs, largely related to vomiting or discomfort, were reported from the two combined trials

Pivotal Trial F38-13/14. This trial reported the largest number of AEs = 21. Two of the AEs were serious, though not listed as such by Braintree; both occurred in Center 1 (Mobile). Patient 19 was randomized to 4L NuLYTELY, developed severe vomiting, was seen in an ER and treated with intravenous fluids and phenergan; Patient 77 took the 4 bisacodyl tablets (20 mg) and 4 h later developed bright red blood per rectum. Both cases resolved. As seen in the next Braintree Table 13 (Page 31, Vol. 1.5) , there was a difference in the number of AEs reported from Center 1 and Center 2. The majority, i.e., 67%, of AEs occurred in Center 2.

Table 13
Adverse On-Therapy Experiences
(Braintree Protocol F38-13/14)

PT#	Center	Bowel Prep	Expect?	AOTE and Comment
9	1	4L	yes	Vomiting: mild. Recovered.
10	1	4L	yes	Vomiting, weak dizzy: Mild. Recovered.
14	1	2Lb	yes	Vomiting: after drinking 1L. Recovered.
19	1	4L	yes	Vomiting: severe. Hospitalized, exam cancelled. Recovered.
26	1	4L	yes	Vomiting: Moderate. Exam cancelled. Recovered.
39	1	2Lb	yes	Vomiting, weakness: Exam cancelled. Recovered.
56	1	4L	yes	Vomiting, bloating, sinus headache: Mild. Recovered.
72	1	4L	NO	Headache: Moderate. Diabetic with Hx high blood sugar. Recovered.
77	1	2Lb	NO	Rectal bleeding: mild. Hx heme positive stool. Recovered.
19	2	4L	yes	Vomiting: Mild. Diary score = 3. Recovered.
22	2	4L	yes	Vomiting: Mild. Diary score = 3. Recovered.
25	2	4L	yes	Vomiting: Mild. Diary score = 3. Recovered.
29	2	4L	yes	Vomiting: Severe. Diary score = 5. Recovered.
32	2	4L	yes	Vomiting: Moderate. Diary score = 4. Exam cancelled. Recovered.
36	2	4L	yes	Vomiting: Mild. Diary score = 3. Recovered.
40	2	2Lb	NO	Iron = 241: poststudy; normalized after.
77	2	4L	yes	Face flushed, runny nose, vomiting: Mild. Possible allergy. Recovered.
82	2	2Lb	yes	Vomiting: Moderate. Diary score = 4. Recovered.
85	2	2Lb	yes	Vomiting: Moderate. Diary score = 5. Anxious patient. Recovered.
89	2	4L	yes	Vomiting: Mild. Diary score = 2. Anxious patient. Recovered.
98	2	2Lb	yes	Vomiting: Mild. Diary score = 2. Recovered.

4L = 4 liter bowel prep; 2Lb = 2L+bisacodyl bowel prep

The combined two center analyses of discomfort with the 2L + bis and NuLYTELY, revealed significantly fewer proportion of patients complaining of nausea, vomiting, and fullness with the 2L + bis. Again, the majority of the cases of vomiting occurred in Center 2. There was no difference between the 2L + bis and NuLYTELY in the proportion of patients complaining of cramps. The fullness, cramping, and vomiting data are illustrated in Braintree Tables 14, 15, and 17.

Table 14
Patient Rating of Fullness
(Braintree Protocol F38-13/14)

Rating	4L NuLYTELY	2L+bis
1 (none)	12.6% (12)	25.0% (23)
2 (mild)	32.6% (31)	56.7% (43)
3 (bothersome)	36.8% (35)	18.5% (17)
4 (distressing)	12.6% (12)	5.4% (5)
5 (severe)	5.3% (5)	4.3% (4)
Mean Score	2.7	2.2
Ridit	0.5	0.356
SE	-	0.03
z	-	4.78
p	-	<0.0001

Table 15
Patient Rating of Cramping
(Braintree Protocol F38-13/14)

Rating	4L NuLYTELY	2L+bis
1 (none)	55.4% (51)	44.6% (41)
2 (mild)	27.2% (25)	43.5% (40)
3 (bothersome)	8.7% (8)	6.5% (6)
4 (distressing)	8.7% (8)	2.2% (2)
5 (severe)	0.0% (0)	3.3% (3)
Mean Score	1.7	1.8
Ridit	0.5	0.475
SE	-	0.03
z	-	0.83
p	-	0.41

Table 17
Patient Rating of Vomiting
(Braintree Protocol F38-13/14)

Rating	4L NuLYTELY	2L+bis
1 (none)	69.1% (65)	86.2% (81)
2 (mild)	9.6% (9)	5.3% (5)
3 (bothersome)	8.5% (8)	1.1% (1)
4 (distressing)	5.3% (5)	3.2% (3)
5 (severe)	7.4% (5)	4.3% (4)
Mean Rating	1.7	1.3
Ridit	0.5	0.416
SE	-	0.03
z	-	3.82
p	-	0.005

Pivotal Trial F38-20. In contrast to the 18 AEs reported in trial F38-13/14, this F38-20 pivotal trial had relatively few AEs, i.e, 6. The patient number, center number, and drug assigned to the six patients who experienced the AEs is depicted in Braintree Table 7 (Page 241, Vol. 1.5). Noticeable in the table are the too unexpected AE (1 with NuLYTELY and with the 2L + bis) both considered minor AEs.

Table 7
Adverse On-Therapy Experiences
Protocol F38-20

Pt #	Center	Prep	Expect?	*Description* and comments
10	3	4L	No	"slight *ache* in back of neck"
45	3	4L	Yes	*Vomiting* - patient could not tolerate prep
141	3	2L+bis	No	*Headache*
159	4	2L+bis	Yes	*Fullness*, nausea rated 5 (severe) on diary
163	4	4L	Yes	*Fullness*, cramps rated 5 (severe) on diary
173	4	4L	Yes	*Vomiting* – unable to tolerate prep

The next Braintree Tables 8, 9, 11 (Tables 242 and 243) show the proportion of patients on 2L + bis and NulYTELY experiencing abdominal fullness, cramping or vomiting. Only abdominal fullness was significantly lower in patients taking the 2L + bis. The comparison of patients experiencing nausea, vomiting and cramping revealed no significant differences between the two drug bowel cleansing preparations.

Table 8
Patient Rating of Fullness
(Braintree Protocol F38-20)

Score	4L	2L+bis
1 (none)	25.3% (25)	37.4% (34)
2 (mild)	41.4% (41)	46.2% (42)
3 (bothersome)	24.2% (24)	13.2% (12)
4 (distressing)	8.1% (8)	2.2% (2)
5 (severe)	1.0% (1)	1.1% (1)
Mean Score	2.2	1.8

$z = 3.42$, $p = 0.005$

Table 9
Patient Rating of Cramping
(Braintree Protocol F38-20)

Score	4L	2L+bis
1 (none)	58.2% (57)	62.4% (58)
2 (mild)	24.5% (24)	31.2% (29)
3 (bothersome)	10.2% (10)	5.4% (5)
4 (distressing)	6.1% (6)	1.1% (1)
5 (severe)	1.0% (1)	0% (0)
Mean Score	1.6	1.4

$z = 3.42$, $p = 0.17$

Table 11
Patient Rating of Vomiting
(Braintree Protocol F38-20)

Score	4L	2L+bis
1 (none)	84.5% (82)	93.4% (85)
2 (mild)	9.3% (9)	3.3% (3)
3 (bothersome)	2.1% (2)	0% (0)
4 (distressing)	4.1% (4)	3.3% (3)
5 (severe)	0% (0)	0% (0)
Mean Score	2.2	1.8

$z = 1.47$, $p = 0.14$

Supporting Trial F38-15. This supportive trial compared bisacodyl 20 mg, 2L Halflyte, and 4L Nulytely. It enrolled 300 patients and 164 completed the bowel cleansing preparation. There were 10 "unexpected" adverse on therapy experiences (AOTES). Patient 11, 51 y female was assigned to 4L and vomited some blood; an UGI endoscopy revealed erosive esophagitis but not Mallory-Weiss. Patient SB (51 y female), fainted and apparently fell after taking the 4 tablets of bisacodyl. She was rescued by her mother and suffered no injuries (MedWatch Report, Page 125, ISS, Vol 1.7). Patient 286, a 57 F, a diabetic enrolled in supporting trial F38-15 (Page 138, Vol. 1.7) called the study monitor 4 h after taking the bisacodyl tablets with hypoglycemic symptoms. Hypoglycemia was confirmed by a blood glucose Accu check of 30 mg/dl. She was advised to eat and the colonoscopy was cancelled. The report states that patient 90, assigned to 2 L Halflytely developed "*irregular beats*" but that "*the subsequent EKG was normal*". My examination of this patient's CFR (Page 117-181, Vol. 1.12), an 80 yF, revealed the patient took the preparation and developed *a "cardiac arrhythmia*" (no specific diagnosis) during EKG monitoring. The lab data showed an elevated magnesium, 111 mg/dl, an LDL of 147 mg/dl, but no other relevant information. An update by Braintree on this patient (6/4/03) revealed that the patient had no EKG abnormalities at the time of discontinuation, and had a history of atrial arrhythmias. Five other "unexpected": AEs consisted of fever, headache and chills. There were 17 adjudicated as "expected" AEs by Braintree, e.g., nausea, vomiting, cramps. In the report, Braintree notes that most of the AEs were recorded "in the second half of the study" (though clarified by the sponsor, this reviewer interprets "second half" as the period after the interim analysis). As described above, Braintree compared the HalLytely Bowel — — and NuLYTELY in incidence of vomiting, cramps and fullness. In this study, the incidence of vomiting, cramps and abdominal fullness was

assessed in patients assigned the components of the HalLytely Bowel [redacted], i.e., 20 bis, 2L HalfLytely and the 4L NuLYTELY. As seen in Braintree Tables 9 and 12, there was significant difference in lower proportion of vomiting and abdominal fullness in patients assigned to the 20 mg bis, over the 2L HalfLytely and NuLYTELY.

Table 9
Patient Subjective Rating of Fullness
(Braintree Protocol F38-15)

Rating (score)	Bisacodyl % (n)	2L Prep % (n)	4L Prep % (n)
1 (none)	60.2% (53)	18.6% (16)	15.2% (14)
2 (mild)	25.0% (22)	44.2% (38)	37.0 % (34)
3 (bothersome)	11.4% (10)	26.7% (23)	28.3 % (26)
4 (distressing)	2.3% (2)	7.0% (6)	14.1 % (13)
5 (severe)	1.1% (1)	3.5% (3)	5.4 % (5)
Mean Score	1.6	2.3	2.6
Ridit	0.243	0.447	0.5
SE	0.031	0.031	0.031
z	8.29	1.71	-
p	<0.0001	0.09	-

Table 12
Patient Subjective Rating of Vomiting
(Braintree Protocol F38-15)

Rating (score)	Bisacodyl % (n)	2L Prep % (n)	4L Prep % (n)
1 (none)	92.1% (82)	81.2% (69)	73.9% (68)
2 (mild)	3.4% (3)	5.9% (5)	5.4% (5)
3 (bothersome)	0.0% (0)	3.5% (3)	5.4% (5)
4 (distressing)	1.1% (1)	5.9% (5)	10.9% (10)
5 (severe)	3.4% (3)	3.5% (3)	4.3% (4)
Mean Score	1.2	1.2	1.7
Ridit	0.294	0.461	0.5
SE	0.031	0.031	0.031
z	2.94	1.25	-
p	0.003	0.21	-

*i. **Reviewer Comments**.*

ix. *The relevant risks with the use of osmotic laxatives and bowel cleansing systems relate to the impact upon serum electrolytes and potential complications from these electrolyte disturbances. My review of the serum electrolytes in both clinical trials revealed no clinically relevant abnormalities of serum sodium, potassium, calcium, magnesium (with one exception of a mild elevation of magnesium in one patient) and serum osmolality. The lower proportion in vomiting observed in pivotal study F38-13/14 may be of some relevance, for persistent retching and vomiting may lead to UGI bleeding, or aggravate potential pre-existing abnormalities, e.g. sudden decrease in blood pressure due to transitory hypovolemia in a predisposed patient (a possible cause of fainting in the aforementioned patient SB), or, the development of hypoglycemia in diabetics (as occurred with patient 286, described above). UGI bleeding due to a tear of a gastric vessel in the gastroesophageal junction is a serious complication of severe vomiting during administration of approved PEG 3350 bowel cleansing systems (Mallory-Weiss Syndrome during GoLYTELY administration). The difference in the proportion of vomiting between the HalfLytely and the 4L NuLYTELY was driven by Center 2. The difference was not replicated in pivotal study F38-20. As mentioned in the above safety description of supportive trial F38-15, one patient did develop UGI bleeding, apparently due to erosive esophagitis.*

x. *The claimed lower incidence of vomiting in patients assigned the HalfLytely bowel Cleansing [redacted], reported in the safety of the two pivotal studies (ISS), was observed only in one of the trials, i.e., F38-13/14. The examination of the F38-13/14 data revealed that observed difference originated solely in one center (Center 2). In the other pivotal trial, i.e., F38-20, the difference did not reach statistical significance. Even if the claimed benefit in vomiting with the 2L HalfLytely + 20 bis is accepted, the vomiting data shown in the above Table 9, from supportive trial F38-15, clearly suggest that the 20 mg bisacodyl tablets, and not the lower 2L PEG, are responsible for the lower incidence of vomiting.*

D. Adequacy of Safety Testing

Overall, the procedures used to evaluate safety in the submitted oivotal and supportive were adequate,

E. Summary of Critical Safety Findings and Limitations of Data

The PRECAUTION section of the label —— *The medical literature has recently referenced two deaths associated with the administration of GoLYTELY (Braintree, MA), recently reported in the literature (Ayus JC et al. Fatal dysnatremia caused by elective colonoscopy. BMJ 326:382-384, 2003). The deaths occurred in US medical centers; both patients were males ages 51y and 73 y, and both patients had end stage renal failure. Apparently, death occurred as a consequence of dysnatremia (hyponatremia or hypernatremia). Though GoLYTELY is a 4L PEG-3350 buffer solution with higher sodium content than NuLYTELY, the exposure to these patients to a 2 L powerful PEG-3350 osmotic agent may prove to be risky and requires clinical judgement. At the time of finalizing this review it is unknown whether additional fatal outcomes have occurred with either GoLYTELY or NuLYTELY. The sponsor is overdue in the submission of the Safety Update, which is required to be submitted 4 months after submission of the NDA application. The precautions should also* —— *The isolated cases of Mallory-Weiss and pulmonary aspiration requires inclusion in the label and attention of health care practitioners.*

F. Safety Update.

Braintree submitted the required safety update on May 12, 2003, nine months after the original NDA submission. The safety update includes 18 adverse drug reports (ADRs) which occurred since September 2002,. The ADRs were associated with the use of PEG-3350 as bowel cleansing systems (Golytely and Nulytely), or with the use of PEG-3350 as a laxative (MiraLax, Braintree). There were 2 ADRs with Golytely, 3 with Nulytely, and 13 with Miralax, Though the majority of the ADRs were non-serious (allergy, vomiting), there were 3 serious ADRs. These included two fatal outcomes.. One death was associated with the use of Golytely, the other fatal outcome was associated with the use of Miralax. The third serious ADR was rectal bleeding from colon diverticuli in a patient who received Golytely. The following narratives were taken from the MEDWATCH reports of the two deaths.

- Mfr #020020 (reported by the patient's mother on September 16, 2002). The patient was a 9 y old male who died on —— According to the report, he had "*life long constipation since age 2 requiring home treatment and hospital admission for washout every 3-4 months, usually with Golytely*", The pediatric gastroenterologist who took care of him felt the

patient had a "*motility disorder*", probably based on an "*abnormal anorectal motility study*". Home therapy included Miralax 17 g tid, lactulose 45 qid, Golytely 8 oz "*daily*" and Fleet's phosphate enemas every 2-3 days. He was admitted 5 days before his death. During his last hospitalization, the outpatient regimen was "*continued along with administration of 5 L of Golytely via nasogastric tube*". An autopsy reported renal failure as the cause of death.

- Mfr #020030 (reported on December 26, 2002). 92 year female with a history of constipation treated with Miralax. A dose of Miralax was taken on —— Two days later, blood was noted after a bowel movement . The patient was transferred to a medical center, where it was determined she was not a surgical candidate. She died of heart failure. The reporter states that the "*medical director (Dr. Scheur) was contacted by phone, and, that Dr Scheur did not feel the death was related to Miralax, and was likely due to the colon cancer*".

Braintree included in the safety update four publications (*Gryspeerdt S et al. Optimisation of colon cleansing prior to computed tomographic colonography. JBR, 85:289-296, 2002. Poon CM et al. Two liters of polyethylene glycol-electrolyte lavage solution versus sodium phosphate as bowel cleansing regimen for colonoscopy. A retrospective randomized controlled trial. Endoscopy, 34:560-563, 2002. Nageshwar Reddy D et al. Efficacy and safety of oral sodium phosphate versus polyethylene glycol solution for bowel preparation for colonoscopy. Indian J Gastroenterol, 21:219-221, 2002. Verghese VJ et al. Low-salt bowel cleansing preparation [LoSo Prep] as preparation for colonoscopy. Aliment Pharmacol Ther, 16:1327-1331, 2002)*). The publications report successful bowel cleansing with either 2L PEG-3350, combinations of PEG-3350 + 10 mg bisacodyl tablets , or magnesium citrate + 20 mg bisacodyl tablets + 1 bisacodyl suppository. There were no serious AEs reported in these studies.

i. Reviewer Comments.

xi. *The submitted safety update is incomplete. Omitted from the update are the two deaths associated with Golytely in patients with end-stage renal disease, reported in the in the February BMJ, 2003. The same article reported the development of tonic-clonic seizures after administration of Golytely in a 62 y female who was on treatment with a diazyde for hypertension. Her serum sodium before colonoscopy was 138 mmol/l and decreased to 116 after colonoscopy. She. required intensive care*

treatment (mechanical ventilation, hypertonic socium chloride) and fully recovered from the serious AE.

xii. *The two deaths reported in this safety update enhances the concern with the use of PEG-3350. In only one case, Golytely was used, off-label. Of relevance, the 90 y patient took Miralax in the recommended dose, but still developed rectal bleeding. Despite one physician assertion, there is no documentation of colon cancer in this elderly lady. These cases further emphasize the need for label information of serious AEs in all PEG-3350 populations, as a class.*

xiii. *It should be noted that patients with renal failure were excluded in the design of the studies cited by the sponsor in the safety update.*

III. Dosing, Regimen, and Administration Issues

No information was submitted on dose ranging to justify the use of the 2L. There was one publication (mentioned in the literature section) of a study showing efficacy with the us of 1.5 L PEG-3350. In spite of these shortcomings, and in light of the clinical comparability shown between the proposed HalfLyte bowel cleansing — and NuLYTELY, the 2L PEG and the 20 mg bis dose appear appropriate doses to achieve efficacy. The proposed package insert provides adequate detail information on drugs administration.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There were more men, i.e., 221, than women, i.e., 179 enrolled in the two pivotal trials F38-13/14 and F38-20. Conversely, there were more women, i.e., 185, than men, i.e., 175 enrolled in the two supportive trials F38-15 and F38-20. Data on efficacy differences by sex was not submitted. Safety data in males and females, related to symptoms caused by the preparations, such as cramping, fullness, nausea, vomiting is displayed in the next Braintree Table 20, submitted by the sponsor on November 25, 2002 (Page 24). As seen, females were significantly less tolerant than males for developing fullness, cramping and nausea during HalfLytely preparation, and in addition, significantly more prone for vomiring during the 4L NuLYTELY administration. .

Table 20 (Revised) – Volume 1.4.4, page 50
Patient Ratings of Symptoms by Sex
(Combined Data)

	Male			Female				
Symptom	n	Ave. Score	% Bother. to Severe	n	Ave. Score	% Bother. to Severe	z	p
Fullness - 2L	94	1.8	13.8	90	2.2	31.1	3.0	**<0.01**
Cramping - 2L	92	1.5	6.5	94	1.7	11.7	2.1	**0.03**
Nausea - 2L	92	1.5	8.7	95	2.0	25.3	3.6	**<0.01**
Vomiting - 2L	92	1.1	3.3	94	1.3	8.6	1.2	0.23
Overall - 2L	93	1.8	14.0	91	2.2	24.2	2.4	**0.02**
Fullness - 4L	117	2.4	45.4	76	2.5	42.1	0.61	0.54
Cramping 4L	114	1.6	14.0	75	1.8	22.7	2.27	**0.02**
Nausea - 4L	116	1.9	25.0	76	2.6	42.2	4.6	**<0.01**
Vomiting - 4L	116	1.3	8.7	74	1.8	21.6	2.6	**<0.01**
Overall - 4L	116	2.2	32.8	74	2.6	44.6	2.58	**<0.01**

2L = 2L+bis

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The November 25, 2002 submission included the next Braintree Table 19 (Page 34). The data compares fullness, cramping, nausea and vomiting during the 2 + bis and 4L preparations in patients younger then 65 y, and older than 65y. With the HalfLytely, a significantly higher proportion of patients patients < 65 y developed fullness, cramping and nausea. In the 4l NuLYTELY, there was similar difference between the two age groups, with addition of more prevalence of vomiting in the <65 y of age.

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Table 19 (Revised) – Volume 1.4.4, page 49
Patient Ratings of Symptoms by Age
(Combined Data)

	<65			65+				
Symptom	n	Ave. Score	% Bother to Severe	n	Ave. Score	% Bother to Severe	z	p
Fullness - 2L	130	2.0	24.7	54	1.9	16.8	1.24	0.22
Cramping - 2L	134	1.7	9.7	52	1.4	7.7	2.5	**0.01**
Nausea - 2L	135	1.8	20.6	52	1.5	7.6	2.5	**0.01**
Vomiting - 2L	134	1.3	8.2	52	1.1	0.0	1.0	0.32
Overall - 2L	133	2.0	19.5	51	1.9	17.7	1.5	0.11
Fullness - 4L	141	2.5	46.1	52	2.2	38.4	1.75	0.08
Cramping - 4L	137	1.7	17.5	52	1.6	17.3	1.00	0.32
Nausea - 4L	140	2.3	35.8	52	1.8	21.1	3.25	**<0.01**
Vomiting - 4L	139	1.6	16.6	51	1.2	5.9	2.05	**0.04**
Overall - 4L	139	2.5	41.0	51	2.0	27.4	2.50	**0.01**

2L = 2L+bis

C. Evaluation of Pediatric Program

The sponsor did not provide information on safety and efficacy of Half Lytely Bowel Prep — in pediatric populations.

D. Comments on Data Available or Needed in Other Populations

No information on populations other than women and elderly was submitted. The review of the Safety Update will determine the need for information on other special population, e.g., renal failure patients.

X. Conclusions and Recommendations

A. Conclusions

The submitted efficacy data revealed comparable efficacy of the Hall Lytely Bowel Prep — to the approved bowel cleansing 4 L NuLYTELY. The overall safety profile of HalfLytely revealed a majority of non-serious AEs, and two serious AEs (hematemesis, rectal bleeding). These AEs resolved spontaneously and were included by the sponsor as non-serious. My assessment of the submitted safety and efficacy of the Half Lytely Bowel Prep — shows an acceptable risk benefit. The sponsor's assessment of the safety data is, however, incomplete. The reported serious AEs associated with

PEG-3350, including death, should be incorporated in the amended label of all PEG-3350-containing bowel cleansing systems.

B. Recommendations

I recommend an approvable action for this NDA application. The reason for my recommendation is the need to incorporate in the label, *prior to a final approval action*, the aforementioned serious AEs reported in the literature and described in this review

Recommended Amendments in the PRECAUTION section, i.e., include statements on the following:

Recommended Amendment in the ADVERSE EVENT section: include statements on the following:

3. Death reported in patients with end stage renal failure, during or after preparation with 4L
4. , tonic-clonic seizures reported in patients taking
5. Development of Mallory-Weiss or UGI bleeding.

The sponsor should also further explain the issue of moneys given tc included in the submitted *Financial Disclosure*.

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/s/

Robert Prizont
6/10/03 12:44:42 PM
MEDICAL OFFICER

Hugo Gallo Torres
6/10/03 01:38:15 PM
MEDICAL OFFICER
The GI MTL agrees with the MO Reviewer recommendation. NDA 21-551 is approvable. The application should be approved once information on seroius adverse events reported with PEG-3350-containing drugs has been included in the proposed labeling.