CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-551/S-013
Priority or Standard	Standard
Submit Date(s)	
Received Date(s)	September 17, 2009
PDUFA Goal Date	July 17, 2010
Division / Office	CDER/OND
Reviewer Name(s)	Zana Handy Marks, MD, MPH
Review Completion Date	
Established Name	HalfLytely and Bisacodyl Tablets Bowel Prep Kit
(Proposed) Trade Name	HalfLytely and Bisacodyl Tablets Bowel Prep Kit
Therapeutic Class	Cathartic/laxative
Applicant	Braintree Laboratories, Inc.
Formulation(s)	Oral solution and tablet
Dosing Regimen	5 mg bisacodyl followed by 2 liters polyethylene glycol (PEG) and electrolyte lavage
Indication(s)	Cleansing of the colon as a preparation for colonoscopy
Intended Population(s)	Adult patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, an approval action is recommended.

1.2 Risk Benefit Assessment

HalfLytely and Bisacodyl Bowel Prep Kit was originally developed to reduce the volume (2 liters) required compared to standard bowel preparations (4 liters) because patient discomfort was associated with the standard 4 liter preparation volume. HalfLytely was improved in 2004 with a bisacodyl dose of 20 mg. However, following the approval of HalfLytely, several reports of ischemic colitis (IC) were received. In May 2006, HalfLytely labeling was revised to include reports of ischemic colitis (IC). The Applicant hypothesized that the IC reports were related to the dose of bisacodyl (20 mg) included in the kit. Therefore, the Applicant submitted an efficacy supplement reducing the dose of bisacodyl from 20 mg to 10 mg. This efficacy supplement was approved in 2007. Data used to support this labeling change demonstrated equivalent efficacy between the preparations 88% HalfLytely with 20 mg bisacodyl (H20) compared to 87% HalfLytely with 10 mg bisacodyl (H10) and demonstrated improved adverse event profile (e.g., decreased abdominal cramping).

In the approval letter for the HalfLytely and Bisacodyl (10 mg) Bowel Prep Kit supplement the FDA requested that additional studies be performed to evaluate lower doses of bisacodyl (7.5 mg, 5 mg and/or 2.5mg). Therefore, the Applicant submitted a clinical study comparing HalfLytely with 5 mg of bisacodyl to the approved HalfLytely with 10 mg of bisacodyl for bowel cleansing preparation prior to colonoscopy in adults.

Although the risk of ischemic colitis is low (about 1 in 100,000 for the H20 prep) it appears to be markedly reduced by the dose reduction to 10 mg. Therefore, further reduction in the dose of bisacodyl without subsequent reduction in efficacy supports a favorable risk benefit profile for HalfLytely with Bisacodyl (5 mg) Bowel Prep Kit.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food, Drug, and Cosmetic Act (FDCA) the Agency is authorized to require the submission of a REMS (Risk Evaluation and Mitigation Strategy) by the Applicant if it has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks

(section 505-1(a)(1)). Based on the potential for serious adverse events including fluid and electrolyte aberrations, seizures, renal impairment, cardiac arrhythmias nausea and vomiting , and ischemic colitis. Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since HalfLytely® and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablet) was approved on September 24, 2007, we have become aware of new safety information derived from clinical trial data related to a class effect regarding fluid and electrolyte disturbances that can lead to serious adverse events, including cardiac arrhythmias, seizures and renal impairment from clinical trial data. We consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

In accordance with section 505-1(a) of the FDCA, we have determined that a REMS is necessary for HalfLytely® and Bisacodyl Tablet Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablet) to ensure that the benefits of the drug outweigh the risk(s) described above.

As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that HalfLytely® and Bisacodyl Tablet Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablet) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of HalfLytely® and Bisacodyl Tablet Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablet). FDA has determined that HalfLytely® and Bisacodyl Tablet Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablet) is a product for which patient labeling could help prevent serious adverse effects.

1.4 Recommendations for Postmarket Requirements and Commitments

Previous studies have evaluated bisacodyl alone compared to 2L and 4L PEG solutions. However, there has not been a study of 2L PEG solution plus bisacodyl vs. 2L PEG solution alone. In the Applicant’s previous studies no significant differences have been seen between 2L PEG plus 20 mg bisacodyl, 2L PEG plus 10 mg bisacodyl, and 2L PEG plus 5 mg bisacodyl. Given the absence of any dosage

response for bisacodyl, the contribution of bisacodyl in this combination product can be questioned. Therefore, a head-to-head comparison should be performed to evaluate whether bisacodyl is necessary.

Clinical Post Marketing Commitment Study 1: Conduct a prospective, 3-arm trial evaluating HalfLytely with 5 mg bisacodyl, 2L polyethylene glycol solution plus electrolytes without bisacodyl, and 4L polyethylene glycol solution plus electrolytes without bisacodyl. The trial should evaluate the pharmacokinetics, efficacy and safety of each regimen in cleansing the colon as a preparation for colonoscopy in adults. Collect pharmacokinetic data in a subset of patients.

The following three postmarketing requirements were PREA requirements reviewed and approved by the Pediatric Review Committee (PeRC):

Study 1: A Retrospective Survey of Colonoscopy Rates in the Pediatric Population

Study 2: A randomized, single-blind, multicenter dose-ranging study to obtain pharmacokinetic data and to compare the safety and efficacy of HalfLytely and Bisacodyl Tablet versus NuLYTELY in children (6-11 years of age).

Study 3: A randomized, single-blind , multi-center dose-ranging study to obtain pharmacokinetic data and to compare the safety and efficacy of HalfLytely and Bisacodyl Tablet versus NuLYTELY in children (birth - 5 years of age).

PeRC recommended deferring Pediatric studies until the application for the adult study was approved. Study 3 will be conducted if data from Studies 1 and 2 supports evaluation of HalfLytely and Bisacodyl Tablet in younger pediatric subgroups.

1.5 Summary of Clinical Findings

1.5.1 Brief Overview of Clinical Program

Study F38-27 was conducted as a randomized, parallel, multi-center, single-blind study. The objective of this study was to evaluate the safety and efficacy of HalfLytely with 10 mg bisacodyl (H10) to HalfLytely with 5 mg bisacodyl (H5) in outpatients requiring colonoscopy for routinely accepted indications. The active control was approved H10. The study medications were provided to patients in identically labeled packages. The only difference in the test preparations was the number of bisacodyl tablets (two versus one) contained inside the kit.

308 patients who met the inclusion and exclusion criteria were randomly assigned in a 1:1 ratio within the 6 participating centers to either receive H5 or H10. 82 of these patients were elderly. 295 patients took the study medication and were included in

the Intent-to-Treat (ITT) analysis. 290 of the 295 patients that took their study medication fully completed the study. Study completion was defined as patients that had a colonoscopy.

1.5.2 Efficacy

The primary efficacy endpoint was based on the colonoscopist's assessment of colon cleansing using a four point scale (poor, fair, and good, excellent). For the primary efficacy analysis, grades 3 (good) and 4 (excellent) were considered "successful" and grades 1 (poor) and 2 (fair) were considered "failure". Failing scores also included any patient exposed to the preparation who was not examined due to an adverse event, non-compliance, or lack of efficacy. The response rate for successful cleansing (4) and (3) was similar between the two treatment groups with 78% for H5 and 80% for H10. The results in Table 1 below represent the cleansing score by treatment group .

Table 1: Efficacy Responder Analysis

Score	H5 n (%)	H10 n (%)
4 Excellent	26 (18%)	23 (16%)
3 Good	88 (60%)	94 (64%)
2 Fair	22 (15%)	22 (15%)
1 Poor	9 (6%)	6 (4%)

The secondary endpoints assessed whether the cleansing for each colonoscopy examination was adequate for visualization and whether the cecum was reached. The response rates for both of these evaluations supported the adequacy of the cleansing preparation in 90% of the examinations.

1.5.3 Safety

295 patients were evaluated in the safety analysis. Due to the nature of the preparation regimen, H5 and H10 patients had similar exposures of short duration (about 6 hours) to the HalfLytely kit. The H5 patients received 50 % of the bisacodyl dose (5mg) as compared to H10 patients (10 mg). At visit 2 prior to the scheduled colonoscopy, patients completed a symptom scale questionnaire which asked them to provide an overall rating of their preparation related symptoms of stomach cramping, stomach bloating, nausea, and overall discomfort. Patients used a five point scale for each symptom where a score of 1= "None", 2 = "Mild", 3 = "Bothersome", 4 = "Distressing", and 5 = "Severely distressing" Patients were also asked to document any vomiting episodes on their treatment questionnaires. There

were no differences in treatment emergent adverse reports observed for the general population based on age, gender, race, or medical risk.

As expected for a drug in this class, the most frequent reports involved gastrointestinal complaints generally consistent with the use of a bowel preparation. The majority of these reports was mild in intensity and resolved quickly. Patient symptom ratings of cramping, bloating, nausea and overall discomfort were generally lower with H5. No difference in vomiting episodes was detected. Reports of severe symptoms (those rated by patients as "bothersome to severely distressing") were reported as being 50% lower for H5 patients for bloating and cramping.

One non fatal serious adverse event was reported during this study. A 55 year old female with a history of abdominal pain and urolithiasis undergoing colonoscopy was reported as having colonic biopsies consistent with ischemic colitis.
There were no deaths reported during the study.

2 Introduction and Regulatory Background

2.1 Product Information

Proposed Trade Name (established name): HalfLytely and Bisacodyl Tablets Bowel Prep Kit (PEG 3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed release tablets).

The HalfLytely and Bisacodyl Tablets Bowel Prep Kit includes:

- PEG_3350 (polyethylene glycol 3350): a large molecular polymer, soluble in a 2 liter buffer solution of sodium chloride, sodium bicarbonate and potassium chloride
- One 5 mg bisacodyl delayed release tablet

Proposed Indication: For cleansing of the colon as a preparation for colonoscopy in adults.

Proposed Age Group: Adults

Pharmacologic Class: Purgative (stimulant laxative and osmotic agent)

Proposed Treatment Regimen: On the day prior to colonoscopy, swallow one 5 mg bisacodyl delayed release tablet with water, wait for bowel movement (or maximum of 6 hours), then drink the HalfLytely solution (prepared as directed) at a rate of 8 ounces every 10 minutes, until completion of the 2 liters.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are two classes of bowl preparation products approved and marketed in the United States: polyethylene glycol (PEG 3350) based products and phosphate-based products (see Table 2).

Approved Peg-based products include GoLytely, Colyte, NuLytely, TriLyte, Moviprep and HalfLytely (with 10 mg bisacodyl). Approved sodium phosphate products include Visicol and oral sodium phosphate solutions (OSPS) and are sold over the counter (OTC). OsmoPrep is an approved oral sodium phosphate tablet product that also contains PEG (8000). See Table 2 below.

Table 2: Approved colon preparation products in the United States*

Drug	Sponsor	NDA #	Approval Date	Ingredients
GoLytely	Braintree	19-011	7/84	PEG 3350+ Electrolytes
Colyte	Schwartz Pharma	18-983	10/84	PEG 3350+ Electrolytes
Oral Sodium Phosphate Solution(OSPS)	Multiple	N/A[1]	N/A[1]	Sodium Phosphate (30 grams) + Fluid
NuLytely	Braintree	19-797	4/91	PEG 3350 + Electrolytes
Visicol	Inkine	212-097	9/00	Sodium Phosphate (60 grams) + Fluid
TriLyte	Schwarz Pharma	ANDA 76-491	2/04	PEG 3350 + Electrolytes Generic
HalfLytely Bisacodyl Kit	Braintree	21-551	5/04	PEG 3350 + Electrolytes+ Bisacodyl (20 mg)
OsmoPrep	Inkine	21-892	3/06	Sodium Phosphate (48 grams) + PEG 8000
MOVIPREP	Norgine BV	21-881	8/06	PEG 3350 + Electrolytes + Vitamin C

1= Oral Sodium Phosphate Solutions (OSPS) are approved under OTC monograph regulations.
Reference: Adapted from Clinical Moviprep NDA 21-881 Review, dated 3/30/06, current product labels and http://www.accessdata.fda.gov/scripts/cder/drugatfda/.
* Includes both over the counter (OTC) and prescription bowel preparation products

2.3 Availability of Proposed Active Ingredient in the United States

HalfLytely and Bisacodyl Tablets Bowel Prep Kit is composed of two active ingredients: PEG 3350 and bisacodyl. The currently marketed formulation of HalfLytely and Bisacodyl Tablets Bowel Prep Kit in the United States contains a bisacodyl dose of 10 mg. The proposed HalfLytely and Bisacodyl Tablets Bowel Prep Kit product contains a 5 mg dose of bisacodyl.

PEG 3350 is the main component of several bowel preparations and is also the active ingredient in Miralax and Glycolax (generic Miralax, a PEG based product approved for the treatment of occasional constipation). Bisacodyl is widely available in the United States, as both an approved prescription product as well as an OTC product.

2.4 Important Safety Issues With Consideration to Related Drugs

As with all drugs in this class, PEG-ELS solutions bear potential risks with use. These can include fluid shifts resulting in serious fluid and electrolyte abnormalities , seizures, renal impairment, cardiac arrhythmias, nausea and vomiting. The use of bisacodyl combined with PEG-ELS solution has been associated with cases of ischemic colitis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following section provides a timeline of important regulatory activity related to the current HalfLytely and Bisacodyl Tablets Bowel Prep Kit submission:

- **May 2004-** The HalfLytely and Bisacodyl Tablets Bowel Prep Kit was originally approved with bisacodyl dose of 20 mg. The Applicant became aware of post-marketing adverse events of ischemic colitis (IC) and cramping with use of the 20 mg kit.

- **February 2005-** A Proposed Pediatric Study Report (PPSR) was submitted for HalfLytely and Bisacodyl Tablets Bowel Prep Kit. This submission received an Inadequate Pediatric Study request (IPSR) on June 24, 2005, due to deficiencies in the protocol. The deficiencies included lack of a statistical analysis plan (SAP), lack of equal representation of patients of all ages, and failure to include patients less than 12 years.

- **May 2006-** The Post marketing section of the HalfLytely label was revised to include ischemic colitis (IC). The Applicant submitted an application to reduce the dose of bisacodyl to 10 mg.

- **August 2006-** A second PPSR was submitted. This submission received an IPSR letter on March 8, 2007, due to concerns of ischemic colitis in adults using this product. FDA recommendations included: 1) Reduce the bisacodyl dose to 5 mg or less in children < 12 yrs. 2) Establish safety and efficacy in older children before initiating studies in younger children. 3) Establish a data safety monitoring board. 4) Use an active control design powered to detect superiority of PEG 2L with bisacodyl over PEG 2L alone to establish safety and efficacy in the pediatric population.

- **September 2007-** HalfLytely was approved with a 10 mg bisacodyl dose. The 20 mg bisacodyl product was removed from the market.
  Four post-marketing commitments were negotiated as part of the approval for the H10 kit:
  1) Deferred pediatric study under PREA for cleansing of the colon as a preparation for colonoscopy in pediatric patients ages birth to 16 years.
  2) Conduct a retrospective study comparing and evaluating the occurrence of ischemic colitis following colonoscopy preparations, such as 4 liter PEG-ELS, to HalfLytely and Bisacodyl Tablets Bowel Prep Kit containing 20mg bisacodyl.
  3) Conduct a retrospective study comparing and evaluating the occurrence of IC following colonoscopy preparations, such as 4 liter PEG-ELS, to HalfLytely Bisacodyl Tablets Bowel Prep Kit containing 10mg bisacodyl. Conduct analyses 6 months, 12 months, 18 months, and 24 months after initial marketing of HalfLytely and Bisacodyl Tablets Bowel Prep Kit containing 10 mg bisacodyl.
  4) Conduct a dose-response study evaluating lower doses of bisacodyl (e.g., 7.5 mg, 5 mg, and/or 2.5mg) for efficacy and safety in cleansing the colon as a preparation for colonoscopy in adults.

- **July 2008-** The third PPSR was submitted and received an IPSR June 2009 due to continued concerns about IC in adults using this product. It was also recommended that the Applicant provide additional information from the post-marketing commitments #2, #3, #4. (see bullet above).

- **December 2008-** Safety and Efficacy Relisting Petition for HalfLytely and Bisacodyl Tablets Bowel Prep Kit with 20 mg bisacodyl concluded that the 20 mg bisacodyl product was withdrawn from market for reasons of safety on September 25, 2007. The determination was made in accordance with 21CFR314.161 and in response to a consult request received from the Office of Regulatory Policy (ORP). ORP generated the consult in response to a citizen's petition submitted by Foley and Lardner, LLP. The petition usually indicates that a person is interested in submitting, has recently submitted, or is awaiting approval of an ANDA for this drug product.

- **September 2009-** Efficacy supplement NDA/013 was received. This supplement compared the efficacy of HalfLytely with 5 mg bisacodyl compared to the approved 10 mg bisacodyl product.

- **December 2009-** In the 74 Day Letter, the Agency requested the completed pediatric study F38-25 and their pediatric plan. The pediatric study and the pediatric plan were submitted December 22, 2009. The Applicant requested a waiver for children ≤ 6 yrs.

- **March 2010-** The Pediatric Plan submitted to comply with PREA requirements for NDA021551/S-013 was found insufficient. However the pediatric study F38-25 was sufficient to address the requirement to study HalfLytely with bisacodyl 5 mg in pediatric patient's ages 12-17 years.

- **May 2010-** The following recommendations were made in response to the HalfLytely and Bisacodyl Tablet Bowel Prep Kit pediatric plan:

    1) Develop an age-appropriate pediatric formulation (or formulations) that contain less than 5 mg of bisacodyl for use in studying pediatric patients ages 0 through 11 yrs.
    2) Conduct a study evaluating an age –appropriate formulation of HalfLytely with bisacodyl for effectiveness, safety, and pharmacokinetics in cleansing of the colon as a preparation for colonoscopy in pediatric patients ages 6 through 11 years.
    3) Following the study in patients 6 through 11 years, conduct a study evaluating an age-appropriate formulation of HalfLytely with bisacodyl for effectiveness, safety, and pharmacokinetics in cleansing of the colon as a preparation for colonoscopy in pediatric patients ages 0 through 5 years.

The justification of a waiver for patients age 0 through 5 years was not convincing and the Applicant was asked to submit additional information such as data on the number of colonoscopies performed in the age group to support the justification.

2.6 Other Relevant Background Information

HalfLytely and Bisacodyl Bowel Prep Kit was originally developed to reduce the volume (2 liters) required compared to standard bowel preparations (4 liters) because patient discomfort was associated with the standard 4 liter preparation volume. HalfLytely was improved in 2004 with a bisacodyl dose of 20 mg. Three Studies F38-20, F38-26 and F38-27 were reviewed to support the original HalfLytely and Bisacodyl Bowel Prep Kit approval and subsequent dose-related changes. All three studies utilized an identical responder definition where colonoscopies were scored by the investigator for cleansing using a four point scale (poor, fair, good and excellent) where grades good and excellent were considered "successful" and grades poor and

fair were considered “failure”. Additionally, failing scores included any patient exposed to the preparation who was not examined due to adverse events, non-compliance or lack of efficacy.

The primary responder results for the three studies for “successful” preparations are compared in Table 3 below.

Table 3: HalfLytely Study Comparison. All “Successful” Responders

Study	4L	H20	H10	H5
F38-20	79% (77/98)	79% (73/92)	-	-
F38-26	-	88% (196/223)	87% (192/221)	-
F38-27	-	-	80% (117/146)	78% (114/147)

Responder results for the study F38-27 are similar to the results of previous HalfLytely studies. The number of successful preparations for either treatment was similar and well within the variability of previous HalfLytely studies. Non-inferiority analysis demonstrated that HalfLytely and Bisacodyl Tablets (5 mg) Bowel Prep Kit (H5) was not inferior to H10 (p=0.005) and the preparations are equivalent with respect to the overall physician rating of colon preparation in patients who completed the study because the 95% confidence intervals (-11.9, 6.8) fall within the pre established 15 % margin of equivalence.

There were no statistically significant differences in treatment emergent effects between the two preparation groups. Patient ratings of gastrointestinal symptoms such as bloating and cramping were lower in the H5 prepped group.

As with other drugs in this class, there are similar safety concerns that may potentially be of harm to patients. These concerns include subsequent fluid shifts resulting in fluid and electrolyte abnormalities, seizures, renal impairment and cardiac arrhythmias. Several events of ischemic colitis were reported with the HalfLytely with 20 mg bisacodyl Prep Kit (H20). A review by the Office of Drug Safety and Epidemiology (OSE) concluded “there appears to be a signal for ischemic colitis (IC) possibly associated with the bisacodyl use…Because of the small number of reported cases, a causal association is difficult to determine.” In 2007, H20 was removed from the market after the approval of the Halflytely product with 10 mg bisacodyl (H10). However, three cases ischemic colitis have been reported with the H10 product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Three study sites were selected for Division of Scientific Investigation (DSI) to conduct audits. Site #2 in Orange, California, Site #5 in New Smyrna Beach, Florida, and Site #1 in Anaheim, California. Sites #2 and #5 appeared to have more favorable outcomes for the product. Site #2 also had particularly high success rates overall. Site #1 enrolled the most patients (78 patients out of 290 total).

The Division of Scientific Investigations (DSI) completed a review dated 06/29/2010 and the review notes that there were no concerning issues identified. Therefore, data provided by the Applicant in support of the efficacy and safety application for HalfLytely and Bisacodyl Tablets (5 mg) Bowel Prep Kit is acceptable for review.

3.2 Compliance with Good Clinical Practices

The Applicant states this study was conducted in full compliance with the U.S. Code of Federal Regulations, the International Conference on Harmonization, and the ethical principles set forth in the Declaration of Helsinki. Additionally, the Applicant states that the Investigators and all study staff conducted the study in compliance with the protocol and were responsible for explaining the purpose, nature, and potential risks of the study to each patient. All patients were required to sign an informed consent form prior to study entry.

3.3 Financial Disclosures

The Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, none of the investigators disclosed any proprietary interest in HalfLytely or any significant equity interest in Braintree as defined in 21 CFR 54.2(b). Finally, no investigator was the recipient of significant payments as defined in 21 CFR 54.2 (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no change proposed for the blended powder (PEG-3350, NaCl, KCl, and NaHCO3) for reconstitution, or to the container for the powder blend. The bisacodyl dosage units are also unchanged. The only difference in the proposed kit is that there is now only one unit-dose tablet included in the kit. The bisacodyl tablets for use in the kit (as proposed in this supplement) are identical to those currently used (same supplier, same appearance, same primary packaging).

The CMC reviewer, D. Lewis, Ph.D., recommends approval of the supplement.

4.2 Clinical Microbiology

There were no Microbiology issues with this submission.

4.3 Preclinical Pharmacology/Toxicology

There were no Pharmacology/Toxicology issues with this submission.

4.4 Clinical Pharmacology

There were no Clinical Pharmacology issues with this submission.

4.4.1 Mechanism of Action

Bisacodyl is a poorly absorbed stimulant laxative which acts to stimulate peristalsis in the colon resulting in stool evacuation. The HalfLytely solution is a PEG-ELS lavage that creates an osmotic diarrhea that cleanses the colon in preparation for endoscopic procedures.

4.4.2 Pharmacodynamics

There were no pharmacodynamic studies for HalfLytely and Bisacodyl Tablets Bowel Prep Kit included in this submission.

4.4.3 Pharmacokinetics

There were no pharmacokinetic studies for HalfLytely and Bisacodyl Tablets Bowel Prep Kit included in this submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Summary of Clinical Studies

Study	Design	Treatment Groups	Number of Patients
F38-27	R, P, MC, SB study comparing 3 different bowel cleansing preparations	HalfLytely® solution with 5 mg bisacodyl (H5) HalfLytely® solution with10 mg bisacodyl (H10)	148 147
F38-25	R , P, MC, SB study comparing 3 different bowel cleansing preparations	HalfLytely® solution with 5 mg bisacodyl (H5) Half Lytely® solution with 10 mg bisacodyl (H10) 4L NuLYTELY®	49 47 48
F38-BIS	R, P, MC, Open label study comparing 6 different bisacodyl treatments from 2 manufacturers	20 mg, 10 mg, 5 mg 20 mg, 10 mg, 5 mg	6 treatments 15 subjects per treatment 1:1:1:1:1:1

R=randomized; P=parallel; MC=multi-center; SB=single-blind

5.2 Review Strategy

Only one study, An Efficacy Evaluation of 2 Different Bowel Cleansing Preparations in Adult Subjects (F38-27) was originally submitted in this application. However, in the Filing Communication Letter dated November 30, 2009, the FDA asked the Applicant to provide, “The full study report and electronic clinical data sets from your completed Study F38-25 in the pediatric age group 6 to 17 years of age” and “The full study report and electronic clinical datasets from your completed Study F38-BIS in adults.” All of the clinical study reports and datasets were reviewed. The pediatric study F38-25 provides supportive safety data.. The bisacodyl study comparing 6 different treatments from 2 manufacturers was included in this submission as per the Agency’s request and can be found in the Appendix.

A review of the data from the pivotal adult study F38-27 and the pediatric study F38-25 was performed. Each study was reviewed individually by the medical reviewer and compared to the results reported in the Applicant's integrated safety and efficacy reports. The studies were reviewed with equal regard to safety and efficacy.

The sources of clinical data used in this review include the results of the submitted clinical trials with emphasis on the protocols and clinical study reports supporting the use of HalfLytely and Bisacodyl Bowel Prep Kit with 5 mg bisacodyl for cleansing of the colon as a preparation for colonoscopy. Other sources of clinical data reviewed include:

- Current labeling for HalfLytely and Bisacodyl Bowel Prep Kit with 10 mg bisacodyl
- Previous reviews of HalfLytely: HalfLytely with 20 mg bisacodyl compared to 4L NuLytely(F38-20); HalfLytely with 20 mg bisacodyl compared to HalfLytely with 10 mg bisacodyl
- Literature review

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Synopsis- Study F38-27 (Adult study)

Title
An Efficacy Evaluation of 2 Different Bowel Cleansing Preparations in Adult Subjects

Study Period
16 February 2009 to 22 May 2009

Study Centers
The study was conducted at 6 U.S. centers with 308 patients enrolled and 295 patients randomized to treatment. 290 patients completed the study (undergoing colonoscopy defined full study completion).

Study Objective
The objective of this study is to evaluate the efficacy, acceptability, and safety of HalfLytely using two different bisacodyl doses (10 mg and 5 mg), for bowel preparation in normal outpatients requiring colonoscopy for routinely accepted indications.

Study Design
The study was a randomized, parallel, multi-center, single-blind study comparing HalfLytely solution with 5 mg of bisacodyl to the approved HalfLytely solution with 10 mg of bisacodyl for bowel cleansing preparation prior to colonoscopy in adults.

All colonoscopists were blinded to patient treatment. Colonoscopists were not permitted to perform any drug related activities such as randomization, dispensing, drug return, and accountability. Blinded investigators performed colonoscopies according to the site's standard procedures and evaluated cleansing efficacy using a four point scale (see Section 6.1.4).

Medical Reviewer's Comments: The study design is acceptable and consistent with other bowel preparation product studies.

Study patients were provided with a treatment questionnaire to complete over the course of their bowel preparation which recorded 1) the times at which they took their bisacodyl tablets 2) started and completed drinking the solution 3) information on any vomiting episodes and a description of what they ate and drank on the day of the preparation.

Prior to the colonoscopy, patients also completed a symptom scale questionnaire to report their overall experience with the preparation.
Assessment tools included the following :

1) Patient treatment questionnaire
2) 5-point scale patient symptom scale
3) 4-point bowel prep cleansing score

Study Procedures:
Visit 1(Screening)

- Medical history, vital signs, physical exam, and urine pregnancy test as appropriate. No ECG or labs performed
- Patients meeting inclusion/exclusion criteria randomized in a 1:1 ratio at each site
- Informed consent obtained
- Study drug dispensed and preparation instructions discussed

Visit 2 (Final Visit)

- Return for colonoscopy the day after completion of the prep
- Review Treatment Questionnaire and complete Symptom Scale
- Confirm dietary restriction violations
- Discuss adverse events and or medication changes
- Follow up physical exam and vital signs
- No ECG or labs obtained

Treatments
HalfLytely (2 liters) and Bisacodyl Tablets Bowel Prep Kit containing 10 mg bisacodyl (H10) or HalfLytely (2 liters) with 5 mg bisacodyl (H5) were provided to patients in identically labeled kits. Patients were instructed to first take the provided bisacodyl, wait for a bowel movement (or to a maximum of 6 hours) and then begin drinking the solution at a rate of 8 ounces every 10 minutes until completion.

Prior and Concomitant Therapy: no restrictions

Treatment Compliance:
Patients were instructed to return all drug supplies to the clinic at Visit 2. Unblinded staff members performed drug accountability by measuring any remaining HalfLytely and by counting any remaining bisacodyl tablets.

Inclusion Criteria

1. Male or female outpatients who required colonoscopy for the following routine accepted indications:
   - Routine screening
   - Polyp or neoplasm
   - Rectal bleeding
   - Other gastrointestinal bleeding
   - Unknown diarrhea or constipation etiology
   - Anemia of unknown etiology
   - Inflammatory bowel disease
   - Abnormal Endosonography
   - Evaluation of barium enema results
   - Laser therapy
2. At least 18 years of age
3. Good health as determined by physical exam and medical history
4. If female and of childbearing potential, is using an acceptable form of birth control (hormonal birth control, IUD, double-barrier method, depot contraceptive, sterilized, abstinent, or vasectomized spouse)
5. Negative urine pregnancy test at screening, if applicable
6. Patient is mentally competent to provide informed consent to participate in the study

Exclusion Criteria

1. Known or suspected ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or toxic megacolon
2. Impaired consciousness predisposing subjects to pulmonary aspiration
3. Pre-existing electrolyte disturbances such as dehydration or those related to diuretic use
4. Known clinically significant electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia
5. Pregnant, lactating, or intending to become pregnant during the study
6. Refusal of a pregnancy test if of child bearing potential
7. Allergies to any of the preparation components
8. Inability to follow study procedures per Investigator's opinion
9. Participation in an investigational clinical, surgical, drug, or device study within the past 30 days

Medical Officer's Comments: The inclusion /exclusion criteria are acceptable and are consistent with other bowel preparation product studies.

Efficacy Endpoint Measures
The primary efficacy endpoint was the measurement of the adequacy of bowel cleansing as rated by the colonoscopists after treatment with either H10 or H5. The primary efficacy endpoint was based on the colonoscopist's assessment of colon cleansing using a four point scale. Scores of 3 and 4 (corresponding to Grades good and excellent) were considered "successful" while scores of 1 and 2 (corresponding to Grades fair and poor) were considered "failure". Failing scores also included any patient exposed to the preparation who was not examined due to an adverse event, non-compliance or lack of efficacy (see Table 5).

Table 5: Bowel preparation cleansing score

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 the exam
4	Excellent	No more than small bits of adherent feces or fluid

The secondary efficacy endpoint measures included the colonoscopist's rating of the adequacy of the cleansing, the requirement for re-preparation, and ability to visualize the cecum during colonoscopy. Additional secondary endpoint measures included the patient's assessment of the acceptability of the cleansing preparation and assessment of preparation-related symptoms. These symptoms include nausea, cramping, bloating, vomiting, and overall discomfort.

Medical Officer's comments: The efficacy endpoint measure are acceptable and are consistent with other bowel preparation product studies.

Statistical Methods
The primary analysis was based on the intent to treat population (ITT) and included all randomized patients who received any treatment. Patients that did not undergo colonoscopy because of inadequate preparation, dietary non-compliance, or preparation related adverse events were considered as treatment failures. Patients who took the preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from the efficacy analyses.

Success rate was analyzed using Cochran-Mantel-Hanzel Chi square test adjusting for the effect of the investigator site. The formal hypothesis test result (p-value) for treatment difference was presented together with a one-sided 95% confidence interval for the difference.

Treatment emergent adverse event rates were descriptively presented by body system, preferred term, severity, and relationship to treatment for ach treatment group. For further details on the statistical analysis plan see Dr. Wen Jen Chen's biometrics review.

Results

Efficacy

In this study, the primary endpoint was the response rate to bowel cleansing based on a four point scale where excellent (4), good (3), fair (2), and poor (1). A patient was a successful responder if the colon cleansing was rated by the colonoscopist as excellent (4) or good (3). Table 6 below includes all 290 patients that had a colonoscopy (patients 1060, 1072, and 3026 were not included because they did not undergo a colonoscopy.

Table 6: Preparation Cleansing Response

Score	H5 n (%)	H10 n (%)
4 Excellent	26 (18%)	23 (16%)
3 Good	88 (60%)	94 (64%)
2 Fair	22 (15%)	22 (15%)
1 Poor	9 (6%)	6 (4%)

The response rate for successful cleansing (4) and (3) was similar between the two treatment groups with 78% for H5 and 80% for H10.

Safety

There were no statistically significant differences in treatment emergent effects between the two cleansing preparations. Most of the treatment emergent adverse events were gastrointestinal. However, these were rated as mild to moderate in severity and appeared to be transient, resolving following completion of the preparation.

No laboratory tests or electrocardiograms were performed pre or post study. There were no on study deaths. One H10 patient was hospitalized with urosepsis approximately one month post colonoscopy. The investigator felt this occurrence was not related to the preparation as she had a prior history of urolithiasis. However,

this same patient had biopsy findings consistent with ischemic colitis that was considered possibly related to the preparation by the investigator.

Conclusions
Refer to section 6.1.4 for discussion of responder analysis.

5.3.2 Protocol Synopsis- Study F38-25 (Pediatric study)

Title
A Safety and Efficacy Evaluation of HalfLytely Solution and bisacodyl Tablets vs. NuLytely in the Pediatric Population

Study Period
17 January 2007 to 09 May 2007

Study Centers
The study was conducted at 26 U.S. centers with 148 patients randomized and 145 patients receiving study medication. Ninety-eight patients were between 12 and 17 years of age at the time of enrollment and 47 patients were between 6-11 years of age. There were 133 patients who fully completed the study.

Study Objective
The objective of the study was to evaluate the safety and efficacy of HalfLytely solution and bisacodyl tablets vs. NuLytely as a bowel preparation before colonoscopic examination in the pediatric population.

Study Design
The study was designed as a randomized, parallel, multi-center, single-blind study comparing 3 different bowel cleansing preparations: 1) HalfLytely solution with 5 mg bisacodyl 2) HalfLytely solution with 10 mg bisacodyl and 3) NuLytely.

All colonoscopists were blinded to patient treatment. Colonoscopists were not permitted to perform any drug related activities such as randomization, dispensing, drug return, and accountability. Blinded investigators performed colonoscopies according to the site's standard procedures and evaluated cleansing efficacy using a four point scale (see Section 6.1.4).

Patients maintained a treatment questionnaire during their bowel preparation which recorded the times the preparation was taken, when they had the first BM, and a description of what was consumed orally on the day of the preparation. Prior to the colonoscopy, patients also completed a symptom scale questionnaire to report their overall experience with the preparation.

No safety, data monitoring or special steering or evaluation committees were formed or met during the study period.

Assessment Tools
Assessment tools included the following:

1) Patient treatment questionnaire
2) 5-point scale patient symptom scale
3) 4-point bowel prep cleansing score

Study Procedures
Visit 1(Screening)

- Medical history, vital signs, physical exam, and urine pregnancy test as appropriate
- Chemistry and Hematology
- No ECG
- Patients meeting inclusion/exclusion criteria randomized to subgroups 6-11 years and 12-17 years
- Informed consent obtained
- Study drug dispensed and preparation instructions discussed

Visit 2 (Final Visit)

- Return for colonoscopy the day after completion of the prep
- Review Treatment Questionnaire and complete Symptom Scale
- Confirm dietary restriction violations
- Repeat chemistry and hematology testing
- Follow up physical exam and vital signs
- No ECG
- Follow-up call 7 days post procedure

Treatments
Pediatric approved NuLytely; adult approved HalfLytely and Bisacodyl Tablets Bowel Prep Kit with 10 mg bisacodyl; or HalfLytely solution with 5 mg bisacodyl. Patients receiving HalfLytely were instructed to first take the provided bisacodyl, wait for a bowel movement (or to a maximum of 6 hours) and then begin drinking the solution at a rate of 8 ounces every 10 minutes until completion. NuLYTELY patients were instructed to drink one 8 ounce glass every 10 minutes until the rectal effluent became clear per the approved labeling.

Treatment Compliance
Patients were instructed to return all drug supplies to the clinic at Visit 2. Unblinded staff members performed drug accountability by measuring the remaining amount in the HalfLytely jug and by counting the number of bisacodyl tablets returned. The amount of NuLytely remaining in the jug was also measured.

Inclusion Criteria
1. Male or female pediatric outpatients ages 6-17 who required colonoscopy for the following routine accepted indications:

- Polypectomy
- Rectal bleeding
- Other gastrointestinal bleeding
- Unknown diarrhea or constipation etiology
- Anemia of unknown etiology
- Inflammatory bowel disease

The other inclusion criteria are the same as those for the adult study. Additionally, the parent/guardian to be mentally competent to provide informed consent for study participation. The Applicant did not provide information to determine if patient assent was obtained from the older children.

Exclusion Criteria
Criteria are the same as listed for the adult study. Additionally, patients were excluded from the study if there was a history of parent/guardian-associated compliance problems (e.g., substance abuse); or if the parent/guardian could not return for scheduled visits with the patient.

Medical Officer's Comments: The inclusion /exclusion criteria are acceptable and are consistent with other bowel preparation product studies.

Efficacy endpoint measures

The primary efficacy endpoint was the measurement of the adequacy of bowel cleansing as rated by the colonoscopists after treatment with HalfLytely with 5 mg bisacodyl or HalfLytely with 10 mg bisacodyl. The colonoscopist's assessment of adequate colon cleansing was rated using a four point scale. Scores of 3 and 4 (corresponding to Grades good and excellent) were considered "successful" while scores of 1 and 2 (corresponding to Grades fair and poor) were considered "failure". Failing scores also included any patient exposed to the preparation who was not examined due to an adverse event, non-compliance or lack of efficacy (see Table 5).

The secondary efficacy endpoint measures included the colonoscopist's rating of the adequacy of the cleansing, the requirement for re-preparation,

Medical Officer's comments: The efficacy endpoint measures are acceptable and are consistent with other bowel preparation product studies.

Statistical Methods
The primary analysis was based on the intent to treat population (ITT) and included all patients randomized and receiving any treatment. Patients that did not undergo colonoscopy because of inadequate preparation, dietary non-compliance or

preparation related adverse events were considered failures. Patients that took the preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from the efficacy analyses. Patients that did undergo colonoscopy had a determination of cleansing success based on the colonoscopists' score of cleansing.

Non-inferiority hypothesis was tested for the comparison between the NuLytely group and each HalfLytely group.

- Null Hypothesis H0: NuLYTELY Success Rate –HalfLytely Success Rate ≥ 20%
- Alternative Hypothesis H1: NuLytely Success Rate-HalfLytely Success Rate < 20%

Rejection of the null hypothesis and acceptance of the alternative hypothesis demonstrates the non-inferiority of HalfLytely within the specified 20% clinical difference. In addition, to the two primary hypothesis tests, an exploratory test of equivalence is presented comparing the 5 mg HalfLytely success rate versus the 10 mg HalfLytely success rate. There was no alpha adjustment for these tests.

The colonoscopy success rates were descriptively summarized by each treatment group overall and by race, gender, and age subgroup (6-11, 12-17). The primary endpoint was analyzed by CMH Chi-square adjusted for sites for the specified one-sided non-inferiority test between NuLYTELY and each HalfLytely group.

Results

Efficacy

The primary efficacy variable in this study was the investigator assessment of successful examination, which was based on their rating of colon cleansing (a four point scale ranging from "poor" to "excellent") where scores of "good" and "excellent" were considered successful. The measure also included patients who were not examined due to inadequate cleansing or inability to tolerate the prep. These were rated as failure. This variable has been used in the adult studies which were the basis for approval for NuLYTELY and HalfLytely.

Study results showed that the H5 treatment resulted in 17% more successful preparations than H10treatment in the overall study population (p=0.037). The difference appears to be driven by a sizable difference in successful scores in younger patients (6-11 years) between the H5 and H10 preparations where a 38% difference in favor of the H5 treatment was seen (p=0.016). See Table 7 below.

Table 7: Primary Efficacy Responder Analysis in Pediatric Patients Ages 6-17

Responder	H5	H10	NU	pH5 vs NU	pH10 vs NU	pH5 vs H10
All Patients (n)	49	47	48	0.129	0.656	0.037
Success	86%	68%	73%			
Age 6-11	17	16	14	0.976	0.059	0.016
Success	88%	50%	86%			
Age 12-17	32	31	34	0.092	0.390	0.477
Success	84%	77%	68%			

The secondary efficacy analysis of the endoscopist's determination of adequate cleansing for evaluation showed that cleansing appeared adequate across the treatment groups. See Table 8 below.

Table 8: Cleansing Adequate for Evaluation

	H5	H10	NU	pH5 vs NU	pH10 vs NU
Adequate (n)	48	43	42	1.000	0.7
Yes	44 (92%)	38 (88%)	39 (93%)		

Safety

The majority of treatment emergent Adverse Events (AE) reports were GI symptoms. Nausea and vomiting were the most common. Nausea and vomiting appeared less frequently in the H5 prepped group overall. See Table 9 below.

Table 9: Number of with TEAE's by MedDRA Body Systems and Preferred Term All Patients

Gastrointestinal Disorders	H5 N = 49	H10 N = 47	NU N = 49	pH5 vs NU	pH10 vs NU	H5 vs H10
Abd distension	3 (6%)	4 (8%)	5 (10%)	0.72	1.00	0.71
Abd pain	3 (6%)	8 (17%)	9 (18%)	0.12	1.00	0.12
Anal discomfort	1 (2.0)	0	0	1.00	-	1.00
Nausea	6 (12%)	10 (21%)	9 (18%)	0.58	0.80	0.28
Vomiting	6 (12%)	10 (21%)	6 (12%)	1.00	0.28	0.28

There was no statistically significant difference in the individual treatment emergent events detected in the 6-11 year old patients. See Table 10.

Table 10: Number of Patients with TEAE's by MedDRA Body Systems and Preferred Term Age 6-11

Gastrointestinal Disorders	H5 N = 17	H10 N = 16	NU N = 14	pH5 vs NU	pH10 vs NU	H5 vs H10
Abd distension	0	1 (6%)	3 (21%)	0.08	.32	0.49
Abd pain	1 (6%)	4 (25%)	5 (36%)	0.07	.69	0.18
Anal discomfort	1 (6%)	0	0	1.00	-	1.00
Nausea	2 (12%)	3 (20%)	4 (28%)	0.38	0.68	0.66
Vomiting	2 (12%)	4 (25%)	2 (14%)	1.00	0.66	0.40

There appeared to be no statistically significant differences between the three preps for adverse events in the older patients. All three groups reported similar frequency of gastrointestinal events. See Table 11.

Table 11: Number of Patients with TEAE's by MedDRA Body Systems and Preferred Term Age12-17

Gastrointestinal Disorders	H5 N = 32	H10 N = 31	NU N = 35	pH5 vs NU	pH10 vs NU	H5 vs H10
Abd distension	3 (9%)	3 (10%)	2 (6%)	0.66	.66	1.00
Abd pain	2 (6%)	4(12.9%)	4 (11%)	0.68	1.00	0.43
Apthous stomatitis	0	1(3.2)	0	-	0.47	0.49
Nausea	4 (12%)	7(23%)	5 (14%)	1.00	0.53	0.34
Vomiting	4 (12%)	6 (19%)	4 (11%)	1.00	0.50	0.51

Symptom Scale Reports
Age 6-11
Younger H5 prepped patients experienced milder response to symptoms overall. Cramping was more prevalent in the H10 and NU prepped patients SS = 3 (bothersome) compared to SS = 1.7 (none to mild) in the same H5 prepped group. Stomach bloating and vomiting were similar across treatment groups SS = 2 (mild). Nausea was more prevalent in the NU prep SS = 3 (bothersome) than H5 or H10 SS = 2 (mild). Overall discomfort was reported as mild to bothersome across treatment groups.

Age 12-17
Nausea was reported as bothersome (SS=3) across the three treatment groups. H5 reported less vomiting (SS= 1) compared to (SS=2) mild in H10 and NU prepped patients. Overall discomfort was reported as mild to bothersome across the treatment groups.

Conclusions
The H5 kit provided more successful preparations overall. H10 was inferior to the H5 in both age groups with H10=50%;H5=88% (6-11); H10=77% H5=84.4% (12-17). In 6-11years the H5 kit provided the best cleansing results (p= 0.016).
There were no statistically significant differences in treatment emergent effects between the cleansing preparations.

The H5 preparation was associated with significantly fewer patient reported symptoms of cramping than either the H10 or Nu treatments (p≤ 0.05). The difference was more profound in younger patients (6-11 years) prepared with H5 who reported significantly less cramping and nausea (p≤0.01). There were no on study deaths. There was one serious adverse event of hospitalization due to abdominal pain and vomiting in an H10 patient. These symptoms were pre-existing and attributed to Crohn's disease and a duodenal ulcer.

Overall discomfort was reported similarly across treatment groups regardless of age but overall the H5 prep was tolerated best and the patients in both age cohorts prepped with H5 had a higher treatment response than those in either H10 or NU.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The currently approved product labeling states HalfLytely and Bisacodyl Tablets Bowel prep Kit is indicated for "cleansing of the colon as a preparation for colonoscopy in adults." There are no proposed changes to the currently approved indication statement. However, the Applicant has proposed a lower dose of bisacodyl (5 mg) for the proposed indication.

6.1.1 Methods

Data from Study F38-27 were analyzed to assess the efficacy and safety of the proposed dose change in adults requiring colonoscopy.
The efficacy information available for medical review includes clinical efficacy or outcome measures from one clinical study , F38-27. Efficacy data were available for

290 patients (148 patients randomized to H5 and 147 patients randomized to H10). Section 5.3 describes the design, study population, treatment, objectives and outcome measures, inclusion and exclusion criteria, concomitant medications, pertinent protocol amendments, and statistical plan.

6.1.2 Demographics

A review of the demographic data was performed to evaluate for any possible imbalances in baseline characteristics of the patients enrolled in Study F38-27. There were similar proportions of male and female patients. The average age of study participants was 55 years for the H10 group and 57 years for the H5 group, (age range19 to 87 years). There were 82 patients age 65 or older (44 in the H5 group and 38 in the H10 group), and 19 patients were 75 years of age or older (11 in the H5 group and 8 in the H10 group). The majority of study enrollees were white (83%); 12% were African American and 8% were Hispanic or Latino. The average weight of study participants was 183 pounds for the H10 group and 188 pounds for the H5 group (range 106-294 lbs). There were no demographic related statistically significant differences in major demographic characteristics between the treatment groups (see Table 12).

Table 12: Study Demographics ITT Population

	H5	H10	p[1]
Age (years)[2]			
n	148	147	0.216
Mean (SD)	56.8 (12.1)	55.0 (13.0)	
Gender			
Female	73 (49%)	61 (42%)	0.199
Male	75 (51%)	86 (58%)	
Race			
White	123 (83%)	122 (83%)	0.198
A. Am.	19 (13%)	16 (11%)	
Other	4 (3%)	9 (6%)	
Ethnicity			
Hispanic	8 (5%)	14 (10%)	0.192
Non Hispanic	140 (95%)	133 (90%)	
Weight (lbs)			
Mean (SD)	188 (44)	183 (47)	0.309

(1) p-value from exact Chi-square test for the categorical variables and from an ANOVA with term for treatment for the continuous variables
(2) Age at Visit 1
(3) Percentage for race does not equal 100% since Hispanic or Latino patients may not have reported a race.
Reference Volume 3 Section 14.1.3

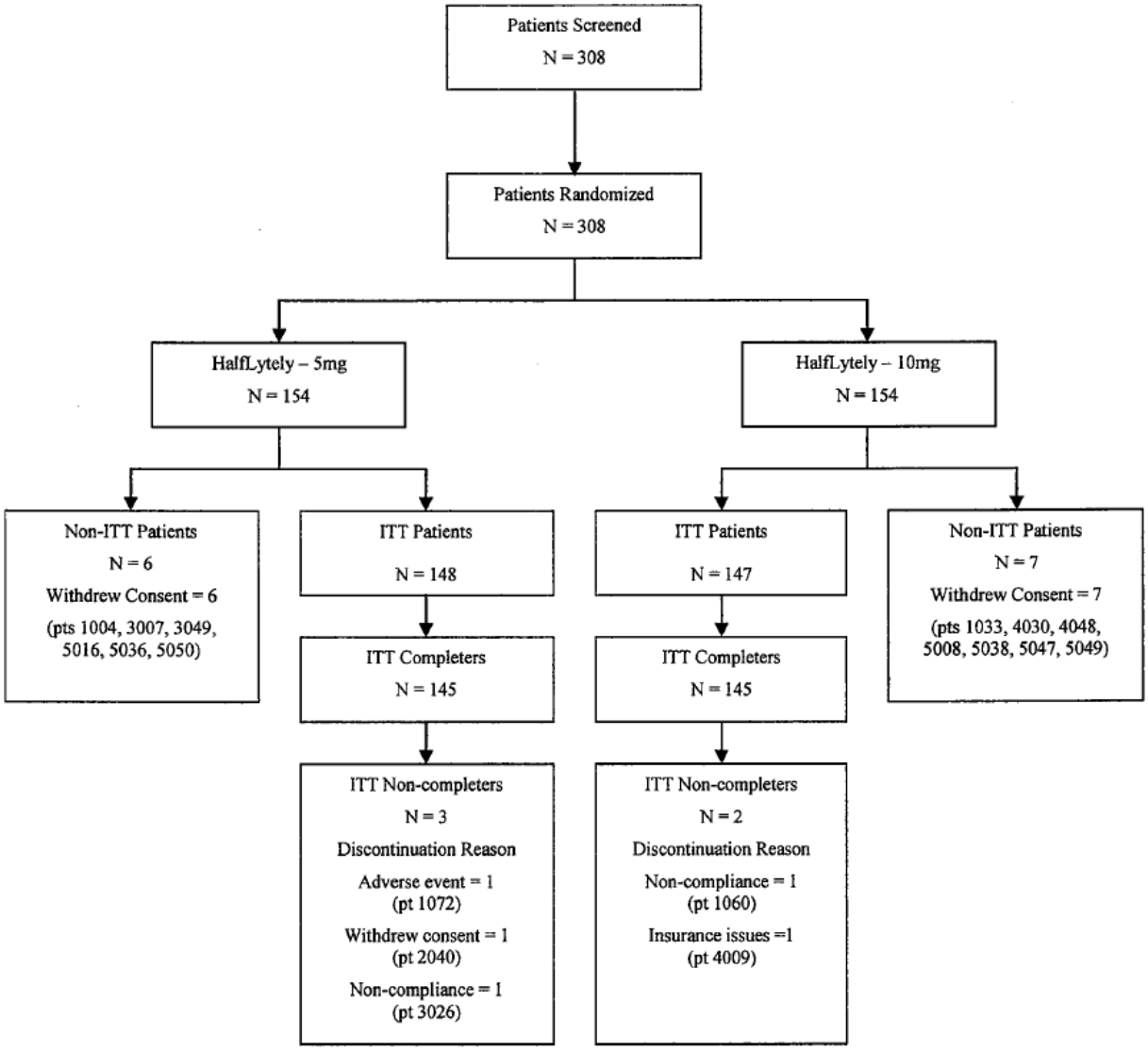
6.1.3 Subject Disposition

The study was conducted at six centers. A total of 308 patients were enrolled. 295 patients took study medication and were included in the intent to treat (ITT) analysis. The majority (290/295) of patients who took the study preparation fully completed the study. Study completion was defined as patients that had a colonoscopy. Five patients (1060, 1072, 2040, 3026 and 4009) took at least a portion of their

preparation but were withdrawn prior to colonoscopy. Patients 1060 (H10) and 3026 (H5) were noncompliant with preparation specific dietary restrictions and were withdrawn, but were included in the efficacy analysis as non-responders. Patient 2040 (H5) was noncompliant with site specific NPO restrictions and decided to withdraw consent and withdrew from the study. Patient 1072 (H5) experienced nausea and vomiting and decided to discontinue the preparation and withdrew from the study. This patient was also included in the efficacy analysis as a treatment failure. Patient 4009 (H10) withdrew from the study prior to colonoscopy due to an "insurance coverage issue" (see Figure 1).

Medical Reviewer Comment: Discontinuations for subjects 1060 and 3026 were due to protocol violations; they did not adhere to the protocol dietary restrictions. The efficacy analysis included patients 4009 and 2040 but excluded 1060, 1072, and 3026. The Applicant did not provide an explanation for this somewhat selective efficacy analysis.

Figure 1: Patient Disposition



(Reference Volume 2; Section 10.1. Page 22)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the measurement of the adequacy of bowel cleansing as rated by the colonoscopists after treatment with either H10 or H5. The primary efficacy endpoint was based on the colonoscopist's assessment of colon cleansing using a four point scale. Scores of 3 and 4 (corresponding to Grades good and excellent) were considered "successful" while scores of 1 and 2 (corresponding to Grades fair and poor) were considered "failure". Failing scores also included any

patient exposed to the preparation who was not examined due to an adverse event, non-compliance or lack of efficacy (see Table 5).

The primary efficacy analysis included 290 patients that underwent colonoscopy as well as three patients that were counted as failures because they could not undergo colonoscopy (patients 1060, 1072, and3026). Two patients (4009 and 2040) were excluded from the responder analysis because they withdrew consent. For details see section 6.1.3 and Figure 1.

A responder was defined as having a successful preparation based on colonoscopist score of 3 (Good) or 4 (Excellent). The efficacy results using the ITT population are presented below in Table 13.

Table 13: Results for Primary Efficacy Responder Analysis Using ITT Population

	HalfLytely and 5 mg Bisacodyl Tablet Bowel Prep Kit (H5)		HalfLytely and 10 mg Bisacodyl Tablets Bowel Prep Kit (H10)		Difference between treatment groups (H5 – H10)	
	% (n/N)	Two-sided 95% CI[1]	% (n/N)	Two-sided 95% CI[1]	Percent Diff %	Two-sided 95% Confidence Interval for Percent Diff
All Patients	78 (114/147)	(69.9, 84.0)	80 (117/146)	(72.7, 86.3)	-2.0	(-11.9, 6.8)
Patients ≥ 65 Years	67 (28/42)	(50.5, 80.4)	61 (22/36)	(43.5, 76.9)	6.0	(-15.8, 26.9)

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4)
(2) Difference between treatments analyzed using Chi-Square Test
(3) P-value for all patients is for the non-inferiority hypothesis using an equivalence margin of 15 percent.

The number of successful preparations between the two treatment groups was similar (H5 78%, H10 80%). Additionally, the Applicant pre-specified a non-inferiority margin of 15%. Using this pre-specified margin, the result was statistically significant ($p = 0.005$), and supports the hypothesis that treatment with H5 is not-inferior to H10 by more than 15%. Additionally, the Applicant asserts that because the confidence intervals reported in the secondary Cochran Mantel Hanzel Chi-Square testing (-11.9,6.8) fall between the pre-determined equivalence margin of ± 15%, H5 can be considered equivalent with respect to cleansing efficacy to the FDA approved H10 control.

However, the Biometrics reviewer, W.J. Chen, Ph.D., does not agree with the Applicant's assertion and argues that, "The applicant did not submit placebo-controlled historical studies including H10 to support the non-inferiority margin of 15%. Since the non-inferiority margin of 15% selected by the applicant was not supported by the well-controlled historical studies conducted under conditions similar

to those planned for the new trial as recommended by ICH E10, the non-inferiority margin of 15% is not acceptable. As a consequence, the non-inferiority of H5 to H10 is not established." The Guidance for Industry for ICH E10 states that, ". . . the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active-control drug would be reliably expected to have as compared with placebo in the setting of the planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. In addition, the margin should also be identified based on past experience in placebo-control trials with adequate design under conditions similar to those planned for the new trial." [1] Since no historical study as recommended by ICH E10 was submitted to support the non-inferiority margin of 15%, the non-inferiority margin of 15% is not acceptable. Accordingly, the non-inferiority of H5 to H10 claimed by the Applicant based upon non-inferiority margin of 15% is not established.

Medical Reviewer's Comment: While Dr. Chen's analysis suggests non-inferiority was not demonstrated statistically, from a clinical standpoint the efficacy results appear to demonstrate H5 provides cleansing that is no worse than and comparable to H10 (78% vs 80%).

6.1.5 Analysis of Secondary Endpoint(s)

The secondary efficacy endpoints for this study were documented with a yes or no response by the colonoscopists to the following questions 1) Was cleansing adequate for evaluation and 2) Was the cecum reached? Cleansing was adequate for evaluation in 91 % of patients in the H5 group compared to 96 % of patients prepped in H10. Additionally, the Applicant asserts that in both study groups the investigators were able to reach the cecum in over 90% of procedures performed in study F38-27. See Table 14 below.

Table 14: Secondary Efficacy Endpoint

Study		H20	H10	H5
F38-26	Adequate			
	Yes	97% (217/223)	99% (217/220)	
F38-27	Adequate			
	Yes		96% (139/145)	91% (132/145)

1 Guidance for Industry E 10 Choice of Control Group and Related Issues in Clinical Trials.pages 4-10.

A non-inferiority margin for the secondary endpoints was not pre-specified. Therefore, a statistical assessment of the similarity of secondary endpoint measurements cannot be determined. However, clinically this information is significant given the fact that the investigators felt the cleansing was adequate for visualization more than 90% of the time for both preparations whether it was rated good or excellent. Presumably the purpose of the colonoscopy was successfully achieved if visualization was this favorable.

6.1.6 Other Endpoints

No other endpoints were analyzed.

6.1.7 Subpopulations

The following table illustrates the overall responder rate for Study F38-27. However the response rate for patients ≥ 65years in the F38-27 study was lower regardless of their treatment and the responder rate. Additionally, H10 results were substantially lower in Study F38-27 (61%) compared to Study F38-26 (86%) (see Table 15).

Table 15: Responder Rates Overall For All Studies

Study		4L Nu	H20	H10	H5
F38-20	All	79% (77/98)	79% (73/92)	-	
	< 65	77% (55/71)	78% (53/68)		
	≥ 65	82% (22/27)	83% (20/24)		
F38-26	All	-	88% (196/223)	86 % (192/221)	
	< 65		87% (151/173)	87% (129/148)	
	≥ 65		90% (45/50)	86% (63/73)	
F38-27	All	-	-	80% (117/146)	78% (114/147)
	< 65			86% (95/110)	82% (86/105)
	≥ 65			61% (22/36)	68% (28/42)

In response to an Information Request sent to the Applicant to explain the lower response rate, the Applicant asserts that the low elderly response overall was attributed to a low response at one site, site 05. No important difference in study site 05 patient demographics or co-morbidities could be determined relative to the other study sites. Re-analysis of F38-27 study data without study site 05 resulted in higher success rates (see Table 16).

Table 16: Primary Efficacy Responder Analysis Excluding Study Site 05

Responder	H5 n (%)	H10 n (%)	p
All Patients Success	122 98 (80%)	123 103 (84%)	0.009
Elderly (≥ 65 yrs) Success	28 20 (71%)	23 17 (74%)	0.687

No important differences were observed between patients at site 05 and other participating sites with regard to dietary infractions or other issues of noncompliance. The lower preparation success in the specified age group did not influence the analysis of the primary endpoint which supported the conclusion that HalfLytely with 5 mg bisacodyl was non-inferior to the approved HalfLytely with 10 mg bisacodyl.

Efficacy analysis based on score and grade
The endpoint was measured using the colonoscopist's assessment of colon cleansing using a four point scale (see Table 4). This endpoint measurement has been used in previous clinical studies to support the approval of other bowel preparations such as NuLYTELY and HalfLytely. For the primary efficacy analysis, grades 3 and 4 were considered "successful" and grades 1 and 2 were considered "failure". Failing scores also included any patients exposed to the preparation who were not examined due to an adverse event, non-compliance or lack of efficacy (see Table 17).

Table 17: Preparation Cleansing Response Study F38-27

Score (Grade)	H5 N (%)	H10 N (%)
4 (Excellent)	26 (18%)	23 (16%)
3 (Good)	88 (60%)	94 (64%)
2 (Fair)	22 (15%)	22 (15%)
1 (Poor)	9 (6%)	6 (4%)

Medical Reviewer's Comments: There is no difference between the successful grades between the cleansing response as defined as successful (excellent + good scores) appears to be similar between the H5 group (78%) and the H10 group (80%). Overlap exists in the definition of the ratings for the Grade of bowel preparation. Additionally, the numerical scores are based on a subjective assessment by the investigator and may lead to both intra-investigator and inter-investigator variability. However, the overall results between the scores of the two preparations are similar.

Comparison between F38-27 results and previous studies

A previous study F38-26 compared the HalfLytely with 20 mg bisacodyl to HalfLytely with 10 mg (NDA 21-551/S006). The Applicant performed an analysis of these preparations compared to H5. The cleansing scores were slightly higher overall in the H20 group compared to the H5 group. There is no difference between the successful grades (excellent + good scores) between the H20 group (88%) and the H10 group (87%) (see Table 18).

Table 18: Preparation Cleansing scores for Studies F38-26 and F38-27

	Score	H20	H10	H5
F38-26	4 (E)	49% (110)	47% (103)	
	3 (G)	39% (86)	40% (89)	
	2 (F)	10% (22)	11% (25)	
	1 (P)	2% (5)	0.9% (2)	
F38-27	4 (E)		16% (23)	18% (26)
	3 (G)		64% (94)	60% (88)
	2 (F)		15% (22)	15% (22)
	1 (P)		4% (6)	6% (9)

(E=excellent; G= good; F= fair; P= poor)

The number of successful preparations for H10 and H5 were similar in study F38-27, and were also similar for H10 and H20 in study F38-26. The review from the original study comparing NuLYTELY to H20 shows the response rate was essentially the same between H20 (78.6%) and the comparator NuLYTELY (79%) see Clinical Review NDA 21551May 17,2003, page 24. This study was the pivotal study for the HalfLytely series and the design, demographics, and endpoints are the same as those for subsequent studies i.e. F38-26 and F38-27. Similarity in design, demographics, and endpoints allow for cross comparisons. Study F38-20 overall response analysis suggests there is no difference in cleansing with using NuLYTELY vs H20. Patient response rates in Study F38-27 demonstrate similar results suggesting that the difference in response rate is not significant 80% (H10) and 78% (H5) between H5 and the comparator H10. (see Table 19).

Table 19: Compared Efficacy for F38-27 and F38-26

Study	4L	H20	H10	H5
F38-20	77% (77/98)	79% (73/92)	-	
F38-26	-	88% (196/223)	86 % (192/221)	
F38-27	-	-	80% (117/146)	78% (114/147)

As a single blinded study, patients knew which drug was used for their bowel preparations. Investigators may have been informed inadvertently about the bowel preparation used by patients. If this occurred, the single blinded trial had the potential to become an open label trial. The fact that there is no treatment by site effect suggests that unblinding in this study was unlikely. The six centers were individually analyzed for the primary efficacy endpoint. Table 20 demonstrates similar results for all sites.

Table 20: Responder Analysis by Site

Site	Score	H5	H10	95% CI	p-value
01	Success	29 (74%)	31 (80%)	-23.8, 13.5	0.789
02	Success	28 (97%)	28 (93%)	-7.9, 14.3	1.000
03	Success	19 (68%)	22 (71%)	-26.7, 20.4	1.000
04	Success	21 (84%)	21 (96%)	-28.3, 5.3	0.352
05	Success	16 (64%)	14 (61%)	-24.3, 30.6	1.000
06	Success	1 (100%)	1 (100%)	-----	----

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

After approval of the H20 bowel prep kit in 2004, the Applicant became aware of rare post-marketing adverse events of ischemic colitis (IC) in association with this kit. In response, the Applicant added a statement concerning ischemic colitis to the Adverse Reactions Section of the HalfLytely labeling and subsequently reduced the dose of bisacodyl in the kit to 10 mg. In the approval letter for the supplement, the FDA requested additional studies be conducted to evaluate lower doses of bisacodyl. Study F38-27 was developed to evaluate the efficacy of a HalfLytely kit containing a 5 mg dose of bisacodyl to the approved kit containing 10 mg bisacodyl. Since the marketing of the H10 kits, 3 cases of ischemic colitis have been reported. One of these cases was on study. No cases of IC were reported from the study with the use of the H5 kit.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable to this submission

6.1.10 Additional Efficacy Issues/Analyses

For additional efficacy issues and analyses please see the Biometrics review provided by Dr. Wen Jen Chen.

7 Review of Safety

Safety Summary

7.1 Methods

The primary safety information for this clinical review includes data from one clinical study, Study F38-27. Additional safety data was submitted to the Agency on 12/17/2009 by the Applicant. The most comprehensive safety data submitted to the application were the safety data collected as part of the GCP-compliant studies (F38-27 and F38-25) Safety data in these studies appear to be adequately collected. Post-marketing safety data collected are not a part of a GCP study and were collected predominantly through spontaneous report of Serious Adverse Events (SAEs).

The Applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA coding system contains greater than 15,000 AE preferred terms that can result in substantial granularity, fragmentation, and dilution of AE terms. AE preferred terms and SOC terms were revised by this Reviewer so that AE terms were clustered together to allow for a more meaningful description of the AE profile of the product (e.g., abdominal discomfort abdominal pain abdominal pain lower and upper, all classified as abdominal pain).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

F38-27 (Adult Study)
295 patients were evaluated in the safety analysis. Due to the nature of the preparation regimen, H5 and H10 patients had similar exposures of short duration (about 6 hours) to the HalfLytely kit. The H5 patients received 50 % of the bisacodyl dose (5mg) as compared to H10 patients (10 mg). Patients took the study medication the day before the colonoscopy. They were contacted 24 hours later for follow-up.

F38-26 (Pediatric Study)
145 patients were evaluated in the safety analysis. H5 and H10 patients had similar exposures of short duration (about 6 hours) to the HalfLytely kit. The NuLYTELY patients were instructed to drink 8 ounces of prep every 10 to 15 minutes until the rectal effluent was clear. No information about the exposure duration to NuLYTELY is included in the study report or appendices. As in the adult study, pediatric patients took the study medication the day before the colonoscopy. They were contacted 24 hours later for follow-up.

7.1.2 Categorization of Adverse Events

As with all bowel cleansing products, the majority of treatment emergent adverse reports were gastrointestinal symptoms including nausea, abdominal cramping, abdominal bloating, and vomiting.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the various studies were not pooled as the types and quality of safety data were variable, and therefore, pooling of data was not performed in this review. Only data from study F38-27 was submitted in electronic datasets. Safety data from other sources including the postmarketing experience were not submitted electronically, and largely consist of case report forms. Therefore, pooling of these data was not performed.

Adverse events were documented similarly for both the adult and pediatric studies. Patients maintained a treatment questionnaire during their bowel preparation which recorded the times the preparation was taken, when they had the first BM, and a description of what was consumed orally on the day of the preparation. Prior to the colonoscopy, patients also completed a symptom scale questionnaire to report their overall experience with the preparation. (see Table 21).

Table 21: Symptom Scale

1	None
2	Mild
3	Bothersome
4	Distressing
5	Severely distressing

Medical Reviewer's Comments: The terms "none", "mild", "bothersome", "distressing", and "severely distressing" used to describe symptom severity are subjective. The Applicant's analysis of only "severely distressing" complaints could potentially underestimate the actual occurrence of an event, because the patient may have experienced an event but to a lesser degree than" severely distressing". Moreover, inter-patient variability in reporting of these subjective complaints may also have affected the results.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Due to the nature of the preparation regimen, H5 and H10 patients had similar exposures of short duration, less than 24 hours as this was a one time bowel preparation. However, the H5 patients received 50 % of bisacodyl (5 mg) as compared to the H10 patients (10 mg). This was true for both the adult and pediatric populations.

7.2.2 Explorations for Dose Response

Study F38-25 was conducted to evaluate the difference in safety and efficacy of the HalfLytely Bowel prep kit using two different doses of the bisacodyl component, 5 mg or 10 mg. Differences with respect to side effects were observed where H5 patients experienced significantly less cramping and nausea.

In the pediatric study group a dose response was also seen in the NuLYTELY group, where patients receiving lower volumes of NuLYTELY solution (≤ 2 liters) experienced 14% fewer successful preparations compared to those receiving higher doses. This is consistent with previous clinical experience of reduced NuLYTELY does in adult studies where 2L was shown to be less effective (73% success) than the full 4L volume (84% success, see NDA (b) (4), Study F38-15)

No dose response of clinical significance was seen in the adult study.

7.2.3 Special Animal and/or In Vitro Testing

No animal or in vitro testing conducted.

7.2.4 Routine Clinical Testing

No routine clinical testing performed.

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, clearance, or interaction workup was conducted in this study.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As with all bowel cleansing products, the majority of treatment emergent adverse reports were gastrointestinal symptoms including nausea, abdominal cramping, abdominal bloating and vomiting. These adverse events have been reviewed previously (NDA 21-551/S-006). In addition, new safety information derived from

clinical trial data related to a class effect regarding fluid and electrolyte disturbances that can lead to serious adverse events including cardiac arrhythmias, seizures, and renal impairment is now available.(Suprep NDA 22-372; Moviprep NDA 021-881).

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in either study.

7.3.2 Nonfatal Serious Adverse Events

Study F38-27 (Adult Study)
There was one report of ischemic colitis in this study. Patient 3005 a 55 year-old white female with a history of urolithiasis and chronic urinary tract infections who was randomized to the H10 group on and received treatment on 3/01/2009 and underwent colonoscopy 3/02/2009. The patient presented to the emergency room six days (3/30/2009) after placement of a ureteral stent complaining of fever, chills, abdominal pain, hematuria and constipation. She was admitted to the ICU, treated with antibiotics, and discharged home on antibiotics. Colonic biopsies in March revealed ischemic colitis. A repeat colonoscopy in May 2009 confirmed resolution of ischemic colitis. Ischemic colitis was assessed by the investigator as being possibly related to the H10 preparation.

Medical Reviewer's Comments: The patient's pre-existing condition of urolithiasis was probably not exacerbated by the bowel preparation as the symptoms preceded the colonoscopy.

Study F38-25 (Pediatric Study)
Patient 11-556, a 16 year-old African American male, was randomized to the H10 group, received treatment on 3/27/2007, and underwent colonoscopy on 3/28/2007. The patient was subsequently hospitalized on (b) (6) with complaints of abdominal pain and vomiting. Esophagogastroduodenoscopy (EGD) and colonoscopy were performed on (b) (6) that revealed Crohn's disease and a duodenal ulcer. The patient was started on mesalamine and steroids 4/17/2007 and was discharged on (b) (6) with improved gastrointestinal symptoms. The investigator assessed that this SAE was not related to the H10 treatment.

Medical Reviewer's Comments: Given the severity of both of the patient's gastrointestinal diagnoses and the fact that both Crohn's and ulcers are usually chronic illnesses it seems highly unlikely that the short duration of exposure to H10 would result in the development of either.

7.3.3 Dropouts and/or Discontinuations

Study F38-27 (Adult Study)
One patient randomized to the H5 group withdrew from the study due to an adverse event. Patient 1072, a 46 year-old female, withdrew from the study after experiencing severe nausea and vomiting which prevented her from completing the treatment. Both events resolved the same day.

Study F38-25 (Pediatric Study)
Seven patients withdrew from the study due to an adverse event. Four female patients randomized to the NuLYTELY group (aged 12-17) discontinued the study. Three patients (10-699, 22-573, 32-616) withdrew due to treatment-related symptoms (bloating, nausea, cramping, vomiting) and one patient (04-639) withdrew due to fever and sore throat. Three patients assigned to the H10 group (10-017, 25-598, and 25-601) withdrew due to treatment-related symptoms (bloating, nausea, cramping, vomiting).

7.3.4 Significant Adverse Events

Study F38-27 (Adult Study)
Significant adverse events were similar for both the adult and pediatric populations. As might be expected from a gastrointestinal cleansing agent, the most significant adverse events included abdominal pain, abdominal cramping, nausea, and vomiting. Other adverse events that may have been related to use of similar drugs in this class were not reported in this study. These include fluid and electrolyte abnormalities, cardiac arrhythmias, renal impairment, and seizures. One patient (H10) with a history of urolithiasis and urinary tract infections had biopsy findings consistent with ischemic colitis.

Table 22 below illustrates the percentage of patients reporting bothersome to severely distressing symptoms. These are the significant adverse events described in this study. Patients were specifically asked about the occurrence of nausea, abdominal cramping, abdominal fullness (bloating), and overall discomfort.

Table 22: Percentage of treated patients reporting "bothersome to "severely distressing" symptoms

	HalfLytely and 5 mg Bisacodyl Tablet Bowel Prep Kit (N=148)	HalfLytely and 10 mg Bisacodyl Tablets Bowel Prep Kit (N=147)
Nausea	12%	14%
Abdominal cramping	5%	11%
Abdominal fullness	5%	14%
Overall Discomfort	13%	15%

In treated patients, reports of bothersome to severely distressing for abdominal fullness and abdominal cramping were more than 50% lower for H5 than H10.

Vomiting as reported in the patient diary was evaluated only if rated as severe. Table 23 below shows the incidence of vomiting in the adult population. See Table 23.

Table 23: Vomiting in the ITT Population

Vomiting N (%)	**H5**		**H10**	
	148	**(%)**	**147**	**(%)**
All Patients	15	10%	10	7%
Age ≥ 65	3	7%	3	8%
Age < 65	12	11%	7	6%
Age > 75	2	20%	1	12%
Males	3	4%	3	5%
Females	12	16%	7	8%
Caucasian	14	11%	7	6%
Non- Caucasian	1	4%	3	12%

Medical Officer's Comments:
Although not statistically significant, patient ratings of expected gastrointestinal symptoms were generally lower with H5, with the exception of vomiting. Although the numbers are small across the studies H5 patients reported more vomiting overall. Vomiting in this drug class of bowel cleansers is a significant adverse event because of the risks to patients of becoming dehydrated. Also, upper gastrointestinal bleeding (Mallory-Weiss tear) has been associated with vomiting during bowel preparation with PEG-ELS solutions. Abdominal fullness and cramping were reported 50% lower in the H5 treated group compared to H10.

High Risk Patients
High risk patients were defined as patients reporting a medical history of cardiac, renal, vascular disease (e.g., hypertension), or diabetes. The following table demonstrates no statistically significant differences in treatment emergent effects adverse events between treatment groups in the high risk patients. H5 patients reported fewer adverse events overall (see Table 24).

Table 24: Number (%) of High Risk Patients with Treatment Emergent Adverse Events by MedDRA Body System and Preferred Term

Body System/Preferred Term[1]	H5 (n=74)	H10 (n=68)	95% CI[2]	p-value
Number (%) of Patients with Any Event	4 (5.4)	7 (10.3)	-13.8, 4.0	0.353
Number of Events	6	11		
GASTROINTESTINAL DISORDERS[3]	2 (2.7)	5 (7.4)	-11.9, 2.6	0.260
Abdominal Distension	0	2 (2.9)	-7.0, 1.1	0.228
Abdominal Pain	1 (1.4)	1 (1.5)	-4.0, 3.8	1.000
Abdominal Tenderness	0	1 (1.5)	-4.3, 1.4	0.479
Anorectal Discomfort	0	1 (1.5)	-4.3, 1.4	0.479
Colitis Ischemic	0	1 (1.5)	-4.3, 1.4	0.479
Nausea	2 (2.7)	0	-1.0, 6.4	0.497
Vomiting	1 (1.4)	0	-1.3, 4.0	1.000
GENERAL DISORDERS	1 (1.4)	0	-1.3, 4.0	1.000
Hypothermia	1 (1.4)	0	-1.3, 4.0	1.000
INFECTIONS AND INFESTATIONS	0	1 (1.5)	-4.3, 1.4	0.479
Urinary Tract Infection	0	1 (1.5)	-4.3, 1.4	0.479
Urosepsis	0	1 (1.5)	-4.3, 1.4	0.479
MUSCULOSKELETAL DISORDERS	0	1 (1.5)	-4.3, 1.4	0.479
Joint Swellling	0	1 (1.5)	-4.3, 1.4	0.479
NERVOUS SYSTEM DISORDERS	1 (1.4)	0	-1.3, 4.0	1.000
Headache	1 (1.4)	0	-1.3, 4.0	1.000
RESPIRATORY DISORDERS	0	1 (1.5)	-4.3, 1.4	0.479
Nasal Congestion	0	1 (1.5)	-4.3, 1.4	0.479
Rhinorrhea	0	1 (1.5)	-4.3, 1.4	0.479

(1) Patients were counted once within each Body System and Preferred Term. (2) 95% confidence interval for difference in proportion and p-value from Fisher's Exact test. (3) Vomiting reported from the patient diary was only included if rated as severe. (reference Table 14.3.1.4, Section 14)

(Reference Volume 2; Section 14 Table 14.3.1.4)

Elderly patients

Analysis of the patient symptom rating for the elderly patients shows that those treated with H5 preparation reported similar cramping, nausea, and overall discomfort as the H10 prepared patients. Elderly patients prepared with H10 reported more bloating than the H5 group (p= 0.008). H5 prepared elderly patients had symptom severity ratings comparable to younger patients (see Table 25).

Table 25: Mean Elderly Patient Symptom Ratings at Final Visit

Symptom	H5 (n=42)	H10 (n=36)	p[1]
Cramping (SD)	1.48 (0.80)	1.44 (0.81)	0.514
Stomach Bloating (SD)	1.29 (0.60)	1.81 (0.86)	**0.008**
Nausea (SD)	1.43 (0.83)	1.53 (0.70)	0.808
Overall (SD)	1.71 (0.84)	1.83 (0.81)	0.656

(Reference Volume 2; Section 14 Table 14.3.6.1)

Gender and Race
With respect to patient reported symptoms, H5 patients tended to report lower symptoms scores regardless of gender, with the difference in bloating favoring H5. This was statistically significant in females (p = 0.030). Analysis of treatment emergent adverse data showed no differences in adverse events by gender or race (see Table 26).

Table 26: Mean Patient Symptom Ratings at Final Visit

Symptom[1]	H5 mean (SD)	H10 mean (SD)	p[2]
Cramping (M)	1.30 (0.49)	1.43 (0.74)	0.566
Cramping (F)	1.61 (0.77)	1.81 (0.86)	0.152
Bloating (M)	1.33 (0.48)	1.62 (0.84)	0.255
Bloating (F)	1.57 (0.66)	1.86 (0.88)	**0.030**
Nausea (M)	1.29 (0.52)	1.44 (0.70)	0.540
Nausea (F)	1.80 (1.12)	1.75 (0.90)	0.831
Overall (M)	1.50 (0.56)	1.70 (0.86)	0.483
Overall (F)	2.01 (0.89)	2.14 (0.91)	0.347

M= male; n= 73 H5 and 61 H10
F =female; n= 75 H5 and 86 H10
Reference Volume 2; Section 14 Table 14.3.6.2

Study F38-25 (Pediatric Study)
The gastrointestinal disorder category had the majority of treatment emergent adverse reports with nausea and vomiting being the most common. No statistically significant differences between preparations with respect to adverse events were detected. Nausea and vomiting were reported less frequently in the H5 group (see Table 27).

Table 27: Number of Patients with TEAEs by MedDRA Body systems and Preferred term All Patients

Gastrointestinal Disorders	H5 N = 49	H10 N = 47	NU N = 49	pH5 vs NU	pH10 vs NU	H5 vs H10
Abdominal distension	3 (6%)	4 (8%)	5 (10%)	0.72	1.00	0.71
Abdominal pain	3 (6%)	8 (17%)	9 (18%)	0.12	1.00	0.12
Nausea	6 (12%)	10 (21%)	9 (18%)	0.58	0.80	0.28
Vomiting	6 (12%)	10 (21%)	6 (12%)	1.00	0.28	0.28

Analysis by age
There was no statistically significant difference in the individual treatment emergent events detected in the 6-11 year old patients. The younger H5 patients reported about half the number of gastrointestinal events compared to the younger H10 and NU patients. See Table 28 below.

Table 28: Number of Patients with TEAE's by MedDRA Body Systems and Preferred Term Age 6-11

Gastrointestinal Disorders	H5 N = 17	H10 N = 16	NU N = 14	pH5 vs NU	pH10 vs NU	H5 vs H10
Abdominal distension	0	1(6%)	3 (21%)	0.08	.32	0.49
Abdominal pain	1 (6%)	4 (25%)	5 (36%)	0.07	.69	0.18
Nausea	2 (12%)	3 (20%)	4 (28%)	0.38	0.68	0.66
Vomiting	2 (12%)	4 (25%)	2 (14%)	1.00	0.66	0.40

There appeared to be no statistically significant differences between the three preps for adverse events in the older patients. All three groups reported similar frequency of gastrointestinal events (see Table 29).

Table 29: Number of Patients with TEAE's by MedDRA Body Systems and Preferred Term Age12-17

Gastrointestinal Disorders	H5 N = 32	H10 N = 31	NU N = 35	pH5 vs NU	pH10 vs NU	H5 vs H10
Abdominal distension	3 (9%)	3 (10%)	2 (6%)	0.66	0.66	1.00
Abdominal pain	2 (6%)	4 (12.9%)	4 (11%)	0.68	1.00	0.43
Nausea	4 (12%)	7 (23%)	5 (14%)	1.00	0.53	0.34
Vomiting	4 (12%)	6 (19%)	4 (11%)	1.00	0.50	0.51

Symptoms Ratings
At Visit 2, prior to the scheduled colonoscopy patients completed a symptom scale questionnaire which asked them to provide an overall rating of their preparation related symptoms of cramping stomach bloating nausea and overall discomfort. Patients used a 5-point scale (1 = none, 2 = Mild, 3 = Bothersome, 4 = Distressing 5 = Severely distressing).

H5 patients had significantly less cramping than either H10 or NU patients, and significantly less overall discomfort than Nu LYTELY. With respect to vomiting, the difference between H5 and the other preps was almost statistically significant in favor of H5 (see Table 30).

Table 30: Mean Patient Symptom Ratings at Final Visit

Symptom	H5 (n=49)	H10 (n=47)	NU (n=48)	H5vNU p[1]	H10vNU p[1]	H5vH10 p[1]
Cramping	1.8 (0.9)	2.4 (1.2)	2.3 (1.2)	**0.047**	0.76	**0.02**
Stomach Bloating	1.9 (1.0)	1.8 (1.0)	2.0 (1.0)	0.85	0.48	0.60
Nausea	2.3 (1.2)	2.7 (1.4)	2.8 (1.3)	0.10	0.83	0.17
Vomiting	1.4 (0.9)	1.8 (1.3)	1.8 (1.2)	0.06	0.95	0.08
Overall	2.4 (1.1)	2.7 (1.3)	2.9 (1.1)	**0.049**	0.43	0.29

(1) p-value for difference between treatments by ANOVA
(Reference Study report F38-26; Volume 2; Section 14 Table 14.3.1)

Analyses of the patient symptom ratings for the two age groups are shown in the tables below (see
Table 31 and Table 32).

Table 31: Mean Patient Symptom Ratings at Final Visit Ages 6-11

Symptom	H5 (n=17)	H10 (n=16)	NU (n=14)	H5vNU p[1]	H10vNU p[1]	H5vH10 p[1]
Cramping	1.7 (0.9)	2.8 (1.4)	3.0 (1.2)	**<0.01**	0.69	**0.01**
Stomach Bloating	1.8 (0.8)	1.5 (0.8)	2.1 (1.1)	0.36	0.14	0.42
Nausea	1.9 (1.0)	2.0 (1.2)	2.9 (1.3)	**0.04**	0.07	0.88
Vomiting	1.6 (1.0)	1.8 (1.4)	1.9 (1.4)	0.45	0.81	0.63
Overall	2.4 (1.0)	2.5 (1.2)	3.1 (1.2)	0.06	0.14	0.77

(1) p-value for difference between treatments by ANOVA
(Reference Study Report F38-26; Volume 2; Section 14 Table 14.3.1.1)

Table 32: Mean Patient Symptom Ratings at Final Visit Ages 12-17

Symptom	H5 (n=32)	H10 (n=31)	NU (n=34)	H5vNU p[1]	H10vNU p[1]	H5vH10 p[1]
Cramping	1.9 (0.9)	2.2 (1.1)	2.0 (1.1)	0.81	0.49	0.32
Stomach Bloating	2.0 (1.1)	1.9 (1.1)	1.9 (0.9)	0.72	0.90	0.82
Nausea	2.6 (1.2)	3.0 (1.3)	2.7 (1.3)	0.61	0.33	0.14
Vomiting	1.2 (0.8)	1.7 (1.2)	1.7 (1.2)	0.06	0.92	0.06
Overall	2.5 (1.2)	2.8 (1.3)	2.8 (1.0)	0.30	0.91	0.31

(1) p-value for difference between treatments by ANOVA
(Reference Study Report F38-26; Volume 2; Section 14 Table 14.3.1.1)

The results in Table 31 show younger H5 pediatric patients experienced milder response to symptoms overall. Cramping was more prevalent in the H10 and NU treatment groups (SS = 3(bothersome)) compared to SS= 1.7 (none to mild) in the same H5 prepped group. Stomach bloating and vomiting were similar across treatment groups SS=2 (mild). Nausea was more prevalent in the NU prep SS=3 (bothersome) than H5 or H10 SS= 2 (mild). Overall discomfort was reported as mild to bothersome across treatment groups.

The results in Table 32 show that the older pediatric patients were generally more tolerant of the H10 and NU preparation. Nausea was reported as bothersome (SS=3) across the three treatment groups. H5 reported less vomiting (SS= 1) compared to SS=2 (mild) in H10 and NU prepped patients. Overall discomfort was reported as mild to bothersome across the treatment groups.

7.3.5 Submission Specific Primary Safety Concerns

A major safety concern with the use of the currently and previously approved HalfLytely with bisacodyl (20 mg and10 mg) Bowel Prep Kit included post- marketing reports of ischemic colitis. Only one patient in the clinical study reviewed developed ischemic colitis (see Section 7.3.2). No reports of ischemic colitis were reported in the clinical studies reviewed.

Since the approval of H10 in September 2007, we have become aware of new safety information derived from clinical trial data related to a class effect regarding fluid and electrolyte disturbances. Fluid shifts and electrolyte aberrations can lead to serious adverse events such as cardiac arrhythmias, seizures and renal impairment.

Safety results from both the adult and pediatric clinical studies appear to demonstrate a decrease in adverse events associated with the lower dose of bisacodyl (5 mg). In the adult study 295 patients received either the H5 or H10 preparation. No significant differences in treatment emergent adverse reports were observed for the general population or on the basis of age, gender, and race. Patients categorized as high

risk showed no statistically significant differences in treatment emergent effects between the two groups. However, within this subgroup, the patients who received 5 mg bisacodyl reported fewer adverse events overall. The most common adverse event reports were gastrointestinal complaints. The majority of these reports were mild to moderate in intensity and resolved.

Medical Reviewer's Comments: Comparatively, the reduced preparation related side effects associated with the H5 preparation in both the adult and pediatric studies compared to the H10 prep and NuLYTELY for pediatrics provides compelling substantive evidence that the dose of 5 mg bisacodyl in the HalfLytely bowel preparation appears to be well tolerated and reasonably safe.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse events for this submission in both the adult and pediatric studies were largely gastrointestinal. They included stomach bloating, cramping, nausea, and overall discomfort. (see Table 33). These symptoms were reported by the Applicant only if they were rated by the patient as "severely distressing". Patients rated their symptoms of cramping, bloating, nausea and overall discomfort using a five point scale where 1="None", 2= "Mild", 3 = "Bothersome", 4="Distressing" and 5 = "Severely distressing". Patients were instructed to rate each of these symptoms on a Symptom Scale questionnaire at the final study visit. Patients generally had a good experience with both preps as indicated by the low average symptom scores ranging between "none" and "mild" (see Table 34).

Table 33: Adverse Reactions Observed in at Least 3% of Randomized Patients

	HalfLytely and 5 mg Bisacodyl Tablet Bowel Prep Kit (N=154)	**HalfLytely and 10 mg Bisacodyl Tablets Bowel Prep Kit (N=154)**
Overall Discomfort	57%	66%
Abdominal fullness	40%	53%
Abdominal cramping	38%	46%
Nausea	34%	42%
Vomiting	10%	7%

Table 34: Mean Patient Symptom Ratings at the Final Visit

Symptom	H5 (n= 148)	H10 (n= 147)	p
Cramping(SD)	1.46 (0.67)	1.65 (0.83)	0.452
Bloating (SD)	1.46 (0.59)	1.76 (0.87)	0.206
Nausea (SD)	1.55 (0.91)	1.62 (0.83)	0.866
Overall (SD)	1.76 (0.79)	1.96 (0.91)	0.500

7.4.2 Laboratory Findings

Blood chemistry and hematology analyses were analyzed before and after the preparation in the pediatric study. The following table shows the change in analyze value (post preparation measurement minus baseline measurement)

There were no statistically significant changes for most analytes. A change from baseline to post preparation was observed for chloride for the H10 vs Nu; but not for H5 vs. NU. This change was small (a difference of 1 mEq/L) and not clinically significant. See Table 35 below.

No laboratory studies were conducted in the adult study.

Medical Reviewer's Comments: Previous study results (F38-20) have shown that bowel cleansing solutions containing PEG 3350 may potentially cause serious electrolyte abnormalities at high doses i.e. 4L. As a cautionary measure chemistries should have been obtained at screening and post preparation (prior to colonoscopy) for these patients taking the reduced dose of 2L PEG 3350 in the HalfLytely kit. This was especially true for patients with pre-existing renal or cardiac problems which may have rendered them more vulnerable to any slight shifts in electrolytes produced by the HalfLytely solution.

Table 35: Mean Laboratory Change in Pediatric Study (post-baseline)

Analyte (SD)	H5 n=49	H10 n=47	NU n=49	p H5vNU[1]	p H10vNU[1]
ALT (U/L)	0.92 (3.7)	4.2 (24.8)	0.5 (4.3)	0.62	0.35
AST (U/L)	2.5 (7.4)	8.1 (48.1)	0.6 (3.6)	0.13	0.32
Bicarbonate (mEQ/L	-0.98 (2.5)	-0.95 (2.6)	-1.9 (2.7)	0.09	0.10
BUN (mg/dL)	-1.8 (3.5)	-2.0 (3.6)	-1.8 (4.3)	0.99	0.83
Calcium (mg/dL)	-0.05 (0.4)	-0.05 (0.5)	-0.09 (0.4)	0.68	0.67
Chloride (mEq/L)	0.48 (2.0)	-0.43 (2.0)	0.74 (2.0)	0.54	**<0.01**
Creatinine (mg/dL)	0.02 (0.1)	0.02 (0.09)	0.02 (0.1)	1.00	0.92
Direct Bilirubin (mg/dL)	0.05 (0.05)	0.06 (0.07)	0.05 (0.05)	0.80	0.29
Hematocrit (%)	-0.48 (2.4)	0.47 (3.1)	-0.27 (2.8)	0.72	0.26
Magnesium (mEq/L)	-0.04 (0.1)	-0.03 (0.2)	-0.07 (0.1)	0.21	0.12
Phosphorus (mg/dL)	-0.07 (0.5)	0.02 (0.5)	-0.22 (0.7)	0.23	0.07
Potassium (mEq/L)	-0.02 (0.5)	-0.08 (0.4)	-0.09 (0.4)	0.49	0.91
Sodium (mEq/L)	0.04 (1.9)	-0.10 (1.8)	0.60 (2.3)	0.21	0.13
Total Bilirubin (mg/dL)	0.25 (0.2)	0.31 (0.4)	0.23 (0.2)	0.65	0.20

(1) p-value is from one-way ANOVA
(Reference Study Report F38-26; Volume 2; Section 14 Tables 14.3.8 and 14.3.9)

7.4.3 Vital Signs

F38-27 (Adult Study)
No statistically significant differences in basic physical examination assessments were observed for either treatment with the exception of diastolic blood pressure. More H5 patients experienced an increase in diastolic BP (94 of 147) compared to H10 (78 of 145 patients). This resulted in a statistically significant difference (p=0.014). Table 36 below highlights these results (see Table 36).

Table 36: Physical Examination Changes (SD) Change from Baseline to End of Study

	H5 (n=148)[1]	H10 (n=147)	p
Weight (lbs)	-2.29 (3.2)	-2.37 (3.5)	0.843
Temperature (°F)	-0.31 (0.72)	-0.22 (0.72)	0.286
Pulse (bpm)	3.31 (10.5)	1.88 (10.3)	0.239
Systolic BP (mmHg)	5.92 (16.9)	3.81 (16.7)	0.284
Diastolic BP (mmHg)	4.88 (11.0)	1.55 (12.1)	**0.014**

(1) Includes only patients that had both pre- and post-treatment assessments
(Reference Volume 2; Section 14 Table 14.3.5.1)

F38-25 (Pediatric Study)
Table 37 shows the change in value between the baseline visit and final visit performed before the colonoscopy. One statistically significant change was observed for pulse H10 vs NU. NU patients experienced an increase in average bpm (about 5). See Table 37 below.

Table 37: Physical Examination Changes (SD) End of Study - Baseline

	H5 (n=49)	H10 (n=47)	NU (n=49)	p[1] H5vsNU	p[1] H10vsNU
Weight (lbs)	-1.0 (2.5)	-1.7 (2.9)	-1.2 (2.3)	0.69	0.32
Temperature (°F)	-0.25 (1.1)	-0.35 (0.9)	-0.25 (1.3)	0.99	0.69
Pulse (bpm)	-0.23 (14.5)	-1.59 (16.4)	5.41 (14.6)	0.07	**0.04**
Systolic BP (mmHg)	0.87 (12.1)	1.5 (12.6)	2.00 (11.6)	0.65	0.85
Diastolic BP (mmHg)	0.34 (10.0)	0.41 (12.2)	-1.45 (9.8)	0.39	0.43

(1) p-value from ANOVA with term for treatment
(Reference Study Report F38-26; Volume 2; Section 14 Table 14.3.7)

Medical Reviewer's Comments: Study F38-27 (Adult) and Study F38-25 (Pediatric) measured blood pressure and heart rate at visit 1 (baseline) and before the colonoscopy at the final visit. In the adult study diastolic blood pressure was increased in the H5 group compared to the H10 group. While this change was characterized as statistically significant, it is doubtful that a change in diastolic blood pressure of approximately 3 mmHg is clinically significant. The 5 bpm pulse increase in the NU patients compared to the H10 patients in the pediatric study is most likely not clinically meaningful.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed at screening and post colonoscopy in the pediatric study. Results were not provided in the datasets. No ECGs were performed in the adult study.

Medical Officer's Comments: ECGs should be performed as part of the screening process and post preparation prior to colonoscopy. For clinical studies involving medications that can potentially induce fluid shifts resulting in electrolyte abnormalities and acute volume changes, ECGs should be standard of care.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant did not perform a QT/QTc study for this NDA. There were no other studies to evaluate specific safety concerns.

7.4.6 Immunogenicity

HalfLytely is not a protein and does not demonstrate evidence for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable

7.5.2 Time Dependency for Adverse Events

Not applicable

7.5.3 Drug-Demographic Interactions

Not applicable

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

The HalfLytely trials did not have any unequivocal drug-drug interactions. Oral medication administered within one hour of the start of administration of HalfLytely solution may be flushed from the gastrointestinal tract and the medication may not be

absorbed properly. Bisacodyl tablets should not be taken within one hour of taking an antacid.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The proposed HalfLytely dosage regimen is for short-term use, less than 24 hours, as such, human carcinogenicity studies were not required.

7.6.2 Human Reproduction and Pregnancy Data

There was no HalfLytely exposure in pregnant women. Women of child bearing potential who had a positive urine pregnancy test, refused a urine pregnancy test, or were planning to become pregnant during the study period were excluded from the study.

7.6.3 Pediatrics and Assessment of Effects on Growth

The duration of the drug exposure is less than 24 hours as this is a one time preparation for bowel cleansing prior to colonoscopy. As such, no assessments of effects on growth were conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

All of the patients in Study F38-27 were instructed to take 2 liters of HalfLytely solution and either 5 or 10 mg of bisacodyl. According to compliance data all patients took either the recommended dose or less than the recommended dose.

Medical Officer's Comments: Ingestion of more than the recommended dose of HalfLytely solution may lead to severe electrolyte aberrations, dehydration, and possibly hypotension related to hypovolemia. Using more than the recommended dosage of bisacodyl in conjunction with HalfLytely solution increases the frequency of common adverse events and may increase the risk of ischemic colitis.

All laxatives and purgative s have the potential for abuse by patients with eating disorders such as anorexia nervosa and bulimia. Additionally, persons interested in "colonics" and colon cleansers could potentially abuse this product.

7.7 Additional Submissions / Safety Issues

There are no additional submissions or safety issues.

8 Postmarket Experience

Additionally, a postmarketing safety evaluation was conducted to assess the incidence of ischemic colitis for the HalfLytely with Bisacodyl Bowel Prep Kit. The following information was provided in a safety review by A. Mackey, Office of Surveillance and Epidemiology (OSE), dated June 10, 2009. This review of postmarketing data obtained from the Adverse Events Reporting System (AERS) and literature showed 22 cases of ischemic colitis possibly associated with HalfLytely solution with 20 mg bisacodyl and related products. AERS was searched using HalfLytely, PEG 3350, bisacodyl, and sodium phosphate as drug names and colitis ischemia as a MedDRA Preferred Term from December 21, 2005 (the date of a previous review) to May 8, 2009. The term “ischemic colitis (IC)” was explicitly used to search the AERS database for possible diagnosis or any endoscopic or histologic evidence of ischemic change or necrosis. This review was updated by OSE May 11, 2010, and included three cases of IC associated with HalfLytely or bisacodyl/PEG combination use. One case was based on findings reported in the literature. The remaining two cases were submitted by a physician reporter who instructed both of these patents to use bisacodyl tablets in addition to the bisacodyl tablets (10 mg) in the HalfLytely bowel preparation kit. These three cases are described below:

1. ***Literature***: The literature was searched using HalfLytely, bisacodyl, and IC as search terms from May 8, 2009 (date of previous search) to May 11, 2020. The search identified one foreign case involving a 68-year-old male who developed two separate episodes of IC after using 10 mg bisacodyl/PEG 2 L combination for bowel cleansing. Five years earlier, a screening colonoscopy found polyps, one of which was found to have a carcinoma *in situ*; he had used 4 L of PEG for cleansing and had no problems. A year later he used bisacodyl 10 mg/PEG 2L for bowel cleansing and experienced left-sided abdominal pain and hematochezia; the colonoscopy found segmental colitis at the splenic flexure and the biopsy was consistent with IC. Two years later he used bisacodyl 10 mg/PEG 2L as a bowel preparation and again experienced IC. Three years later, he used PEG only as a bowel preparation and had no problems.2 (The author of this report was contacted to obtain dosage information for bisacodyl and PEG. The report is pending.)

2. A 50-year-old female experienced cramping, rectal bleeding, and fever after taking 15 mg of bisacodyl and 2 L PEG as a bowel preparation before colonoscopy (reason for colonoscopy was not stated). Since she was experiencing an adverse event, her physician told her not to take the bisacodyl tablets (10 mg total) from the HalfLytely kit. She was diagnosed with IC in the splenic flexure per colonoscopy; a biopsy was consistent with IC. Treatment and outcome were not reported. Her concomitant

medications included topiramate, perindopril erbumine, fexofenadine, estrogen, esomeprazole, ibandronate, and triamcinolone acetonide nasal spray. Her medical history included bladder lift and hysterectomy; she had no history of IC.

3. A 45-year-old female with a history of resection due to colon cancer experienced cramping after taking 10 mg of bisacodyl and 2 L PEG as a bowel preparation before colonoscopy for routine surveillance. Because she was experiencing cramps, her physician told her not to take the bisacodyl tablets (10 mg total) from the HalfLytely kit. IC was noted in the splenic flexure and confirmed by pathology. Treatment for IC was not reported; the patient recovered from the event. She had no history of IC. Her concomitant medications were reported as calcium and multivitamin.

According to the OSE review the majority of the IC cases reported to AERS and the literature have involved the 20 mg bisacodyl dose used with PEG. This updated review describes 3 cases of IC associated with 10 mg bisacodyl/2L PEG and one report of IC associated with 15 mg bisacodyl/ 2L PEG. It appears that in two cases, the treating physician advised the patients to take bisacodyl tablets in addition to the 10 mg bisacodyl provided in the HalfLytely kit. Physician-tailored bowel cleansing regimens are common in clinical practice and as such, off-label use of higher bisacodyl doses may be expected. Additionally, cases of IC or IC-like symptoms may be under reported because IC is a labeled event. Furthermore, bisacodyl has been on the over-the-counter (OTC) market for over 40 years for the treatment of constipation. Until 2007, there were no reporting requirements for non-NDA OTC products, so there could be additional reports of IC associated with bisacodyl use. Based on AERS cases, and literature reports, there appears to be an association between ischemic colitis and use of bisacodyl and PEG combination products used as a bowel preparation before colonoscopy. Therefore, this reviewer recommends that physicians instruct patients to use the HalfLytely with Bisacodyl Bowel Prep Kit according to the instructions provided in the labeling without additional treatment to “facilitate” cleansing.

9 Appendices

5.3.3 Protocol Synopsis – Study F38-BIS

Title
A Pilot Evaluation of 6 Different Bisacodyl Treatments in Adult Subjects

Study Period
Not given

Study centers
The study was conducted at 2 US centers with 90 patients enrolled and randomized.

Study Objective
To evaluate if reduced doses of bisacodyl would produce a bowel movement within 6 hours after drug administration while improving related symptoms. This pilot study compared three dose levels of bisacodyl from two different manufacturers for rapid laxative effect and associated symptoms.

Study Design
The study was a randomized, parallel group, open label study comparing three dose levels of bisacodyl from two different manufacturers for rapid laxative effect and associated symptoms

Study Duration
7 days. Participants were randomized to one of six groups at the screening visit if they met the inclusion/exclusion criteria. Subjects took assigned bisacodyl and returned to the clinic within 6 days after the screening visit.

Treatments
The bisacodyl treatments included three dose levels from each bisacodyl manufacturer ((b) (4)). The treatments evaluated were a single administration of bisacodyl from either (b) (4) or (b) (4) consisting of: 5 mg (one 5 mg tablet), or 10 mg (two 5 mg tablets), or 20 mg (four 5 mg tablets). Subjects were assigned to one of six possible treatments in a ratio of 1:1:1:1:1:1 (15 subjects per treatment).

Inclusion Criteria
Male or female at least 18 years of age in good health as determined by medical history and physical exam. If female, and of child bearing potential, they had to be using an acceptable form of birth control and have a negative urine test.

Exclusion Criteria
Subjects were excluded if they had known or suspected ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or toxic megacolon, or constipation; refusal to discontinue laxatives or prokinetic agents during the study: pregnant, lactating, or intending to become pregnant during the study; refusal of a pregnancy test if applicable, allergy to bisacodyl

Efficacy endpoint measures
Primary – the time required to produce a bowel movement within 6 hours after drug administration

Secondary- Assessment of treatment related symptoms of nausea, cramping stomach bloating, vomiting, and overall discomfort, and patient acceptability.

Statistics
No statistical analysis was performed for this pilot study. Data was summarized in descriptive tables.

Results
Efficacy
Ninety study subjects were enrolled and randomized to six different groups in a 1:1:1:1:1:1 fashion. Patients ranged in age from 18-84 with the average age being 45. Study group included 57 females and 33 males. The majority of the patients were White.

Study subjects were given a single dose of the laxative and asked to record the time of each bowel movement (BM) and associated symptoms. Most study subjects in the three (b) (4) treatment groups had at least one bowel movement within 6 hours after ingesting their bisacodyl dose. Bisacodyl from (b) (4) appeared to give more variable results. At each dose level, a higher percentage of patients had a BM after (b) (4) bisacodyl. See Table 38 below.

Table 38: Patients with BM ≤ 6 Hours

Dose	(b) (4) (n = 15/dose)	(b) (4) (n = 15/dose)
5 mg	13 (88%)	10 (67%)
10 mg	15 (100%)	7 (47%)
20 mg	13 (88%)	12 (80%)

(b) (4) bisacodyl appeared to induce the first BM slightly faster than bisacodyl from (b) (4) at the lower doses 10 mg (O) 2.4hrs vs. (TC) 5Hrs. The time to BM was similar at 5 mg (O) 4hrs vs. (TC) 4.4hrs; and 20 mg (O) 3.8hrs vs. (TC) 3.6hrs. No dose response with respect to time to first BM after taking 5, 10, or 20 mg bisacodyl was demonstrated.

Safety
Mean subject symptom scores for bowel movements indicate that symptoms were generally mild and that there were no substantial differences between doses or manufacturers. No vomiting was reported except for one subject who reported distressing symptoms after taking 20 mg of (b) (4) bisacodyl. See Table 39 below.

Table 39: Treatment Associated Symptoms

Dose	Cramping (n= 15/dose)		Bloating (n= 15/dose)		Nausea (n= 15/dose)	
	(b) (4)					
5 mg	1.7	1.0	1.3	1.2	1.2	1.0
10 mg	1.3	1.1	1.2	1.4	1.1	1.0
20mg	1.4	1.4	1.4	1.2	1.3	1.0

Symptom score: 1=none; 2=mild; 3=moderate; 4=distressing; 5=severely distressing

Conclusion
This pilot study in 90 healthy subjects demonstrated no dose response with respect to taking 5 to 20 mg of bisacodyl. Fewer subjects taking (b) (4) bisacodyl had a bowel movement within the required 6 hour window. In this respect the (b) (4) bisacodyl provided a more reliable result. (b) (4) bisacodyl was associated with a slightly more overall discomfort at the 20 mg dose possibly due to cramping.

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling recommendations are currently under review.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was conducted regarding this efficacy supplement.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21551	SUPPL-13	BRAINTREE LABORATORIES INC	HALF LYTELY BISACODYL BOWEL PREP KIT

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

/s/

ZANA H MARKS
07/16/2010

DONNA J GRIEBEL
07/16/2010
Signing as proxy for Lynne Yao, MD in her absence.