

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)/ Office of Drug Evaluation III
Reviewer Name(s)	Zana H. Marks MD,MPH
Review Completion Date	May 19, 2012
Established Name	Sodium Picosulfate
(Proposed) Trade Name	PICOPREP
Therapeutic Class	Bowel Cleansing Agent
Applicant	Ferring Pharmaceuticals
Formulation(s)	Powder for oral solution in a sachet. Each sachet contains the active ingredients sodium picosulfate 10.0 mg, magnesium oxide 3.5 mg, citric acid 12.0 mg
Dosing Regimen	2 sachets administered as a split dose regimen or day before dose regimen
Indication(s)	Colon cleansing in preparation for colonoscopy
Intended Population(s)	Adults

Template Version: [March 6, 2009](#)

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for PICOPREP for the indication of cleansing of the colon as a preparation for colonoscopy in adults. The recommended dose of PICOPREP is 2 pouches of powder for oral solution, each dissolved in 5 ounces of cold water administered at separate times. At least 64 ounces of additional fluids must be consumed. The Sponsor proposes the approval of 2 dosing regimens:

- Split –Dose regimen: The first PICOPREP pouch is taken the night before the colonoscopy, and the second is taken the next day, in the morning prior to the colonoscopy.
- Day-Before regimen: The first PICOPREP pouch is taken in the early afternoon or early evening and the second is taken approximately 6 hours later, the night before the colonoscopy.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States, resulting in the second highest rate of cancer related mortality<sup>1</sup> Detection of CRC at an early localized stage is associated with a 5-year survival rate of 90%.<sup>2</sup> Current guidelines recommend colonoscopy, starting at 50 years of age for average risk individuals, as the preferred screening method to promote early detection and removal of polyps and precancerous lesions that may lead to CRC.<sup>3</sup>

Despite the evidence supporting the effectiveness of colorectal screening less than half of the US population aged 50 years and older undergoes screening colonoscopy. Patient reluctance to undergo screening may contribute to low screening rates.

The importance of a high-quality bowel preparation for the detection of polyps has been demonstrated in several studies.<sup>4,5</sup> Patients who are either unable or unwilling to complete a colon-cleansing regimen may have inadequate bowel cleansing, which can result in incomplete visualization of the colon and failure to detect colon

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1 Jemal et al ,Cancer statistics,2010. CA Cancer j Clin.2010;60 :277-300.

2 Eisen,Glen Importance of Split Dosing Bowel Preparation for ColonoscopyGI Digest Volume 1, June 2011.

3 Rex DK et al, American College of Gastroenterology guidelines for colorectal cancer screening 2009. Am J Gastroenterol 2009; 104:739-750.

4 Leaper et al,Reasons for failure to diagnose colorectal carcinoma at colonoscopy. Endoscopy.204;36:499-503

5 Harewood GC et al. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc.2003;58:76-79.

pathology. Furthermore, poor bowel preparation may have a substantial economic impact by prolonging procedure time and increasing the chance of an aborted examination, thereby necessitating a repeat colonoscopy at an interval sooner than that recommended by the guidelines. Therefore, improvements in bowel preparation tolerability are paramount for increasing patient compliance with CRC screening guidelines, which in turn can lead to improved outcomes of colonoscopy.

Split dosing of bowel preparations for colonoscopy has recently emerged as an important factor in bowel cleansing efficacy and may also impact patient tolerability. In an effort to improve the quality of colonoscopy, the 2008 American College of Gastroenterology guidelines for CRC screening recommend that bowel preparations be given in split doses and that this regimen be considered the standard of care.<sup>3</sup>

One of the main concerns with respect to bowel preparations administered entirely the day before the procedure is the potential for impaired visualization of the colon because of residual fecal matter, particularly in the right colon. Passage of chyme from the small intestine to the cecum and ascending colon during the 10 to 14 hours between final administration of the purgative and onset of the procedure may make the visualization of mucosal detail difficult. In addition, continuous gastric, intestinal, pancreatic, and biliary secretions also may result in re-accumulation of small intestinal effluent in the colon.<sup>6</sup>

Another measure of the improved efficacy of a split dose regimen compared with a conventional previous day dosing regimen of bowel preparation is the potentially enhanced detection of nonpolypoid flat lesions.<sup>2</sup> Flat lesions are hard to differentiate endoscopically from normal mucosa because flat lesions present with only subtle differences. These lesions have a greater association with CRC than polypoid adenomas of similar size at the time of detection. Furthermore, the lesions in the right colon are more often flat, which may contribute to the increased incidence of right-sided CRC compared with the overall rate of CRC.<sup>7</sup> In a study evaluating a PM/AM split-dose regimen, dosing the morning of the procedure (AM dosing), and dosing the day before the procedure (PM dosing), both PM/AM and AM dosing demonstrated superior colon cleansing compared with PM dosing.<sup>8</sup> In addition, detection of flat lesions was significantly greater in the PM/AM and AM dosing groups than in the PM dosing groups. These results provide further evidence that improvement in the quality of bowel preparation associated with PM/AM split dosing is associated mainly with the second purgative dose (AM dose) administered the same day as the colonoscopy.

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6 Frommer D. Cleansing ability and tolerance of three bowel preparations for colonoscopy. *Dis Colon Rectum*.1997;40:100-104.

7 Baxter, NN. Association of Colonoscopy and death from colorectal cancer: a population based, case-control study. *Ann Intern Med*.2009;150:1-8.

8 Parra-Blanco A et al. The timing of bowel preparation before colonoscopy determines the quality of cleansing and is a significant factor contributing to the detection of flat lesions: a randomized study. *World J Gastroenterology*.2009;12:6161-6166.

**Reviewer's comment: Using bowel preparations in a split dose can be done with polyethylene glycol electrolyte lavage solution or PEG-ELS, NaP, or oral sulfate solutions. Although other products have been used for bowel preparation in split doses, MoviPrep, OsmoPrep, Visicol, and Suprep are the only formulations approved by the FDA as split dose regimens.**

**Data also suggests that colonoscopies performed within 6 to 8 hours of the end of the preparation were associated with significantly better bowel cleansing than endoscopic examinations performed more than 8 hours after the end of preparation.<sup>9</sup> Split dosing appears to be an effective strategy to optimize colon cleansing. It is also felt that by maximizing the time between the 2 doses, split dosing may minimize the risk of dehydration associated with bowel preparations. Additionally, improving the quality of bowel preparation and potentially the detection of flat lesions especially in the proximal colon, a split dose regimen may increase the efficiency of colonoscopy and CRC screening. This reviewer recommends the split dose regimen be approved as the method of administration for this product. The split dose regimen was superior to HalfLyte in the clinical trials and was not associated with additional safety adverse events despite more frequent electrolyte shifts than the day before regimen. These shifts in electrolytes for both studies were minimal, non persistent , and clinically insignificant.**

## **1.2 Risk Benefit Assessment**

The current recommendation for colonoscopy for individuals of average risk for colon cancer begins at age 50 with follow-up every 10 years thereafter if the procedure does not detect lesions. The potential benefits of products such as PICOPREP provide adequate preparation prior to a colonoscopy permitting better visualization of polyps or cancers in the colon. Early detection of colon cancer can result in more effective treatment and survival advantage. Detection and removal of adenomatous polyps can interrupt their progression to cancer. Suboptimal preparation occurs as often as 25% of cases<sup>10</sup>. It is associated with missed diagnoses and increased cost secondary to prolonged procedure times and repeat exams due to aborted procedures.

Fluid and electrolyte abnormalities are well known risks associated with osmotic bowel preparations. These are labeled in similar products such as Suprep and Moviprep. Ischemic colitis, a rare event emerged as a safety signal in preparations combining bisacodyl + PEG-ELS as a bowel cleansing agent where the amount of bisacodyl was ≥ 10 mg.

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9 Marmo et al. Effective bowel cleansing before colonoscopy: a randomized study of split dosage versus non split dosage regimens of high-volume versus low-volume polyethylene glycol solutions  
Gastrointestinal Endoscopy Volume 72, No. 2: 2010.

10 Jemal A et al, Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010;19(8):1893-907

Review of the current Application reveals that PICOPREP is safe when used as instructed. The benefit of PICOPREP for cleansing of the colon as a preparation for colonoscopy outweighs the risk of its use in an appropriate patient population.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

There is no REMS for this application. There is a Medication Guide informing patients about the risks associated with this drug; side effects that may occur; instructions for preparation and administration; and instructions for notifying the healthcare provider regarding concomitant medications and if any untoward events occur .

### **1.4 Recommendations for Postmarket Requirements and Commitments**

- 1) We recommend that the Applicant perform a thorough QT study.
- 2) PREA requirements are discussed in Section 7.6.3 Pediatrics and Assessment of Effects on Growth of this review.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

PICOPREP™ (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution is indicated for cleansing of the colon as a preparation for colonoscopy in adults.

PICOPREP is provided as a powder in two pouches, the contents of each to be dissolved in 5 ounces (150 mL) of cold water and consumed.

Each pouch contains 16.1 g of powder, which has three active ingredients: sodium picosulfate 10 mg; along with magnesium oxide 3.5 g and citric acid 12 g, which together form magnesium citrate in solution.

Sodium picosulfate is a stimulant cathartic.

- Chemical name: 4,4'-(2-pyridylmethylene) diphenyl bis(hydrogen sulfate) disodium salt
- Chemical formula: C<sub>18</sub>H<sub>13</sub>NNa<sub>2</sub>O<sub>8</sub>S<sub>2</sub>
- Structural formula:

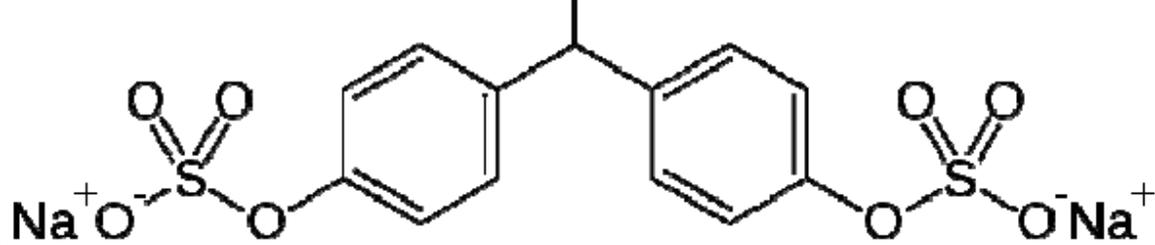
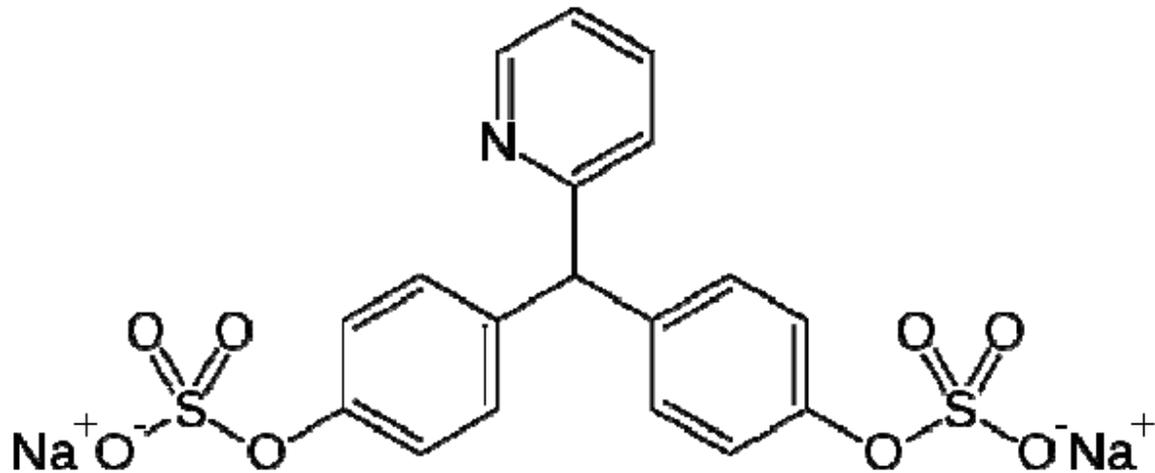


Figure 1 Structural Formula of Sodium Picosulfate



- Molecular Weight: 499.4
- Magnesium citrate is an osmotic laxative.
- Chemical formula:  $Mg_3(C_6H_5O_7)_2$
  - Molecular weight: 214.4

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are several products currently approved by the FDA for bowel cleansing for preparation for colonoscopy. Specific products are included in the table below.

FDA 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
NuLytely	Braintree	19-797	4/91	PEG 3350 + Electrolytes
Visicol	Inkine	212-097	9/00	Sodium Phosphate (60 grams) + Fluid
TriLyte	Schwartz Pharma	ANDA 76-491	2/04	PEG 3350 + Electrolytes Generic
HalfLytely and Bisacodyl Tablets Bowel Prep Kit	Braintree	21-551	5/04	PEG 3350 + Electrolytes + Bisacodyl (20mg)
OsmoPrep	Inkine	21-892	3/06	Sodium Phosphate (48 grams) + PEG 8000
MOVIPREP	Norgine BV	21-881	8/06	PEG 3350 + Electrolytes + Vitamin C
HalfLytely and Bisacodyl Tablets Bowel Prep Kit	Braintree	21-551/S-006	9/2007	PEG 3350 + Electrolytes + Bisacodyl (10mg)
HalfLytely and Bisacodyl Tablets Bowel Prep Kit	Braintree	21-551/S-013	7/2010	PEG 3350 + Electrolytes + Bisacodyl (5mg)
SUPREP Bowel Prep Kit (Na <sup>2+</sup> , K <sup>+</sup> , Mg <sup>2+</sup> sulfate)	Braintree	22-372	8/2010	2 6oz bottles of oral solution Na <sup>2+</sup> sulfate 17.5g, K <sup>+</sup> sulfate, 3.13g, Mg <sup>2+</sup> sulfate 1.6 g

### 2.3 Availability of Proposed Active Ingredient in the United States

PICOPREP is not approved in the United States. Sodium picosulfate is not an approved substance for laxative use or for bowel cleansing in preparation for colonoscopy in the United States. Magnesium citrate, an FDA approved osmotic laxative is available over the counter in the US.

The combination of sodium picosulfate with magnesium oxide and citric acid that is the subject of this application is currently approved for use for colon cleansing in 33 countries around the world. The product, under the trade names Picolax, PicoSalax, Pico-Salax, or Picoprep, is currently marketed in Canada, Australia and United Kingdom.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Colonoscopy is the standard method for evaluation of the colon. Diagnostic accuracy and therapeutic safety of colonoscopy depend on the quality of the colonic cleansing or preparation.<sup>11</sup> For colonoscopy inadequate preparation is responsible for up to a third of all incomplete procedures and precludes 10% of examinations. This outcome negatively impacts the rate of polyp and adenoma detection.<sup>12</sup>

Compounds used for bowel cleansing can be divided into 3 categories according to their mechanism of action: *isosmotic*, *hyperosmotic* and *stimulant*. Their physiologic mechanisms impact the choice of preparation, especially in patients with underlying comorbidities, the elderly and children.

Early “bowel prep” regimens evolved from preparations that were used for radiologic tests and typically involved diet restriction for 2-3 days, enemas, laxatives, and/or large volume (7 - 12L) oral bowel lavage.<sup>13</sup> Historically, these regimens were time consuming, uncomfortable, inconvenient for patients and resulted in fluid and electrolyte disturbances.

This led to the development of *osmotically balanced* solutions formulated to provide minimal water absorption or secretion into the bowel lumen. A polyethylene glycol (PEG) electrolyte lavage solution (PEG-ELS) was originally developed in the early

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11 Wexner et al, A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons(ASCRS), the American Society for Gastrointestinal Endoscopy(ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons(SAGES) , Surg Endosc (2006) 20: 1147-1160.

12 American Society for Gastrointestinal Endoscopy, Technology Status Evaluation Report, Gastrointestinal Endoscopy Volume 69, No.7 :2009.

13 Nelson et al, Technology Status Evaluation Report. Colonoscopy preparations. May 2001. Gastrointest Endosc. 2001;548:29-32

1980s. Since then, several preparations have been introduced to improve palatability and compliance (e.g., sulfate free PEG-ELS). More recent preparations allow for a reduced volume of PEG-ELS but required combination with a stimulant laxative such as bisacodyl or magnesium citrate to ensure adequate colon cleansing.

### ***Isosmotic preparations***

Isosmotic preparations that contain PEG are considered osmotically balanced, high-volume, non-absorbable, and non-fermentable electrolyte solutions. These solutions cleanse the bowel with less water and electrolyte shifts and provide evacuation, primarily by the mechanical effect of large-volume lavage. With sodium sulfate preparations, sodium absorption in the small intestine is largely reduced because of the absence of chloride, the accompanying anion necessary for active absorption against an electrochemical gradient. Low volume PEG preparations are used in combination with stimulant laxatives or ascorbic acid.

### ***Hyperosmotic preparations***

Hyperosmotic preparations draw water into the bowel lumen, which stimulates peristalsis and evacuation. These are smaller-volume preparations but their hyperosmotic nature can cause fluid shifts, accompanied by transient serum electrolyte alterations.

Magnesium citrate is a hyperosmotic agent with additional effects through release of cholecystokinin, resulting in fluid secretion and stimulation of peristalsis. Magnesium citrate has been used in combination with other agents but as a sole agent, has typically been less effective

### ***Stimulant preparations***

Stimulant laxatives promote colonic motility through variable mechanisms that are incompletely characterized.

Bisacodyl is a diphenylmethane derivative that is poorly absorbed in the small intestine and hydrolyzed by endogenous esterases. Its active metabolites stimulate colonic motility, with an onset of action between 6 and 10 hours.

Senna, an anthracene derivative, is processed by colonic bacteria to its active metabolite to stimulate colonic peristalsis. Senna, combined with a liquid diet, has been used as a cleansing agent in children.

Adverse events following bowel preparation are uncommon but potentially serious. Because many patients undergoing screening are healthy, the benefit: risk ratio must be carefully considered when deciding which preparation to prescribe. The adverse effects of bowel preparations are magnified when there is inadequate hydration, inappropriate dosing and inappropriate patient selection<sup>14</sup>

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14 Adamcewicz, M et al Mechanism of Action and Toxicities of Purgatives Used for Colonoscopy Preparation, Expert Opin Drug Metab Toxicol. 2011 January; 7(1): 89-101

Hyponatremia as a result of vomiting, diarrhea, renal disease or inappropriate secretion of ADH can develop with any colonoscopy preparation. Vomiting leads to reduction in plasma volume, an increase in ADH concentration, and increased thirst. Patients with renal insufficiency, hypothyroidism, mineralcorticoid deficiency, liver cirrhosis, heart failure or those on diuretics, NSAIDs, or ACE inhibitors or have an impaired ability to excrete free water and are at increase risk for hyponatremia.<sup>15</sup>

### **Toxicity of PEG Preparations**

Electrolyte disturbances are uncommon with PEG use. Because it is isosmolar, it appears to be relatively safe for patients at risk for electrolyte imbalance and those who cannot tolerate a significant fluid load i.e. renal failure, congestive heart failure or advanced liver disease with ascites. PEG has not been shown to alter histological features of the colonic mucosa and may be used in patients suspected of having Inflammatory bowel disease<sup>16</sup>

GI injuries associated with PEG use include seven reports of Mallory-Weiss tears and three cases of esophageal perforation caused by vomiting following ingestion of PEG-based bowel preparation. Predisposing factors were not identified and all patients recovered after conservative management in the case of the tears and surgical repair for the patients with perforation<sup>17,18</sup>

Rare episodes of mild volume overload have been reported with the use of PEG-ELS in patients with severe congestive heart failure and those with chronic renal insufficiency. In patients with severe left ventricular dysfunction with or without renal insufficiency who are to undergo procedures that necessitate bowel cleansing PEG-ELS is recommended.<sup>4</sup>

### **Toxicity of Osmotic Preparations**

Osmotic bowel preps can cause fluid and electrolyte disturbances. There have been reports of serious adverse events including cardiac arrhythmias, seizures and renal impairment associated with osmotic bowel preps. Risk factors for adverse events associated with fluid and electrolyte disturbances include hypovolemia, baseline kidney disease,

All sodium phosphate NaP preparations have been associated with adverse events. Their use should be limited to patients without cardiac or renal dysfunction, and caution should be exercised when they are administered to patients with pre-existing electrolyte disturbances, patients using medications that affect renal perfusion or function (such as

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15 Chen CD et al, Hyponatremia as a complication of colonoscopy. *Lancet*.2001;357(9252):282-3.

16 Pockros PJ et al Golytely lavage versus a standard colonoscopy preparation. Effect on normal colonic mucosal histology. *Gastroenterology*.1985;88(2):545-8.

17 Brinberg DE et al. Mallory-Weiss tear with colonic lavage. *Ann Intern Med*. 1986;104(6):894-5

18 Eisen GM et al.Esophageal perforation after ingestion of colon lavage solution. *Am J Gastroenterol*.1995;90(11):2074.

diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]. Also caution must be used when considering the use of this product in elderly and debilitated patients.<sup>19</sup>

NaP preparations are associated with changes in electrolyte levels that usually resolve within 24 hours. The most common electrolyte imbalances include increases in phosphate and decrease in calcium. The risk of hyperphosphatemia is higher in the elderly patients. This may be due to an age related decline in renal function. Nephrocalcinosis is defined as a tubular injury with abundant calcium phosphate deposits on renal biopsy. NaP purgatives have been associated with this rare form of kidney injury known as Acute Phosphate Nephropathy. Hypokalemia and hypocalcemia that occurs after NaP use may affect cardiac rhythm by prolonging the QT interval. Ventricular tachycardia associated with hypokalemia during bowel preparation with NaP has been reported in patients with underlying cardiac disease and arrhythmia<sup>20</sup>

Macroscopic and histological changes to the mucosa have been described in patients receiving NaP and other osmotic laxatives as a preparation for colonoscopy. Reports have described aphthoid erosions after cleansing with NaP mimicking those seen in inflammatory bowel disease.<sup>21</sup> Some clinicians avoid the use of NaP preparations in patients suspected of having inflammatory bowel disease. The Warnings and Precautions section of the label for other osmotic cleansers such as SUPREP and MOVIPREP warn that the use of the osmotic laxative products may produce colonic mucosal aphthous ulcerations. The labels also note the potential for mucosal ulcerations resulting from the bowel preparation should be considered when interpreting colonoscopy findings in patients with known or suspected IBD.

The FDA issued an alert about the safe use of oral NaP products. The agency expressed concern about the use of OTC NaP products at the higher doses typically used for bowel cleansing before colonoscopy. A voluntary recall was announced by the manufacturer of these products. The FDA alert also indicated that the manufacturer of prescription NaP tablets would be required to put a black box warning on its product labels. The warning highlights several key concepts related to the use of NaP for bowel cleansing including 1) acute phosphate nephropathy, 2) identifiable patient risk factors for APN including increased age, hypovolemia, increased bowel transit time, active colitis, and baseline kidney disease, and 3) use of certain medications that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors,

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19 Barkun et al, Commonly used preparations for colonoscopy: efficacy, tolerability, and safety—a Canadian Association of Gastroenterology position paper. *Can J Gastroenterol.* 2006;20(11):699-710.

20 Clarkston WK et al, Oral sodium phosphate versus sulfate free polyethylene glycol electrolyte lavage solution in outpatient preparation for colonoscopy: a prospective comparison. *Gastrointest Endosc.* 1996;43(1):42-8,

21 Zwas FR et al Colonic mucosal abnormalities associated with oral sodium phosphate solution. *Gastrointest Endosc.* 1996;43(5):463-6

angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]).

Magnesium citrate an over the counter (OTC) laxative used as an adjunct in bowel cleansing preparation should be used with caution in patients on a low sodium diet. It is recommended that magnesium containing bowel cleansers be used with caution in patients with renal impairment, heart disease, patients on concomitant medications that affect electrolyte balance such as diuretics and in elderly and debilitated patients<sup>4</sup>

**Reviewer's Comment: All purgatives have been associated with adverse events of varying degrees of severity. Age, health status, co morbid conditions, and concomitant medication use are important factors to consider when choosing a bowel preparation for patients. The risk for complications can be minimized by selecting the most appropriate bowel cleansing regimen for each patient and emphasizing the importance of adherence to the preparation instructions.**

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

A Type B, Pre-Investigational New Drug (IND) Application meeting was held on **16 April 2009** to obtain assistance from the Agency regarding the development program for PICOPREP.

The Agency agreed that the overall study designs for the Phase 3 clinical trials (FE2009-01 and FE2009-02) proposed by the Sponsor were similar to those of studies done for bowel preparation products and would be reasonable to conduct with a few modifications:

- The non-inferiority margin was changed from 15% to 9%.
- Timing of safety assessments was amended to include monitoring at the following times: Screening (Visit 1), day of randomization (Visit 2), day of colonoscopy (Visit 3), and 24-48 hours (+1 day), 7 days (+3 days), and 4 weeks (±5 days) after the procedure (Visits 4, 5, and 6, respectively).
- Additional measures were added to ensure blinding: study coordinators were to sign affidavits, the colonoscopists and assistants were instructed not to ask the patients how their bowel preparation was performed, and all colonoscopies were scheduled for the mornings.

The Agency requested that the Sponsor provide information that would be typically generated in Phase 2 studies. This information was well established in existing literature, as well as in recently completed investigator-initiated trials, including a Phase 1 study (C-01) that evaluated the magnitude and time course of serial electrolyte and volume status changes following administration in healthy volunteers and a Phase 2 study (C-02) that evaluated the safety, efficacy, and tolerance in an elderly population

(≥70 years). These data clearly established and supported the size of doses needed, amount of fluids needed, necessary amount of each active component in the formulation, split-dose versus day-before dosing regimens, timing of administration, timing between doses for the day-before dosing regimen, and time needed from completion of preparation before undergoing colonoscopy for the current PICOPREP program under review. The Agency agreed.

Since this product has not been approved in the United States, a thorough QTc study was recommended by the Agency, if picosulfate was greater than minimally bioavailable.

Sodium picosulfate is a locally acting, stimulant cathartic of the triarylmethane class, with a mode of action similar to bisacodyl. Picosulfate is a prodrug, like bisacodyl, with no known pharmacologic activity of its own. In addition, this chemical and pharmacologic class has not been associated with QT/QTc interval prolongation or Torsades de Pointes ventricular tachycardia based on considerable post-marketing surveillance. In keeping with the request, however, the Sponsor agreed to include extensive ECG data collection throughout the Phase 3 studies.

The ECG measurements were determined using standard methods by a central ECG laboratory, consistent with Food and Drug Administration (FDA) Guidance. A quality-control review process was used, and central ECG laboratory cardiologists reviewed 100% of all ECGs. Cardiologists made interpretations of morphology and other parameters.

The Agency requested evidence that each component of PICOPREP makes a contribution to the claimed effect, which typically involves conducting a study using a factorial design. The contribution of each component (sodium picosulfate, magnesium oxide, citric acid) of PICOPREP is well documented in the literature, and supports the benefits of combining sodium picosulfate with 2 substances currently FDA approved for over-the-counter (OTC) chronic use: magnesium oxide and citric acid. When added to water, magnesium oxide and citric acid combine to form magnesium citrate, an FDA-approved, osmotic laxative with an established cathartic effect. In a randomized, prospective, 3-arm study, the Picolax formulation (same as PICOPREP) was shown to provide significantly better bowel preparation than the magnesium citrate formulation (Citramag) ( $p < 0.01$ ).

The difference was most apparent in the ascending colon. The Sponsor therefore declined consideration of a factorial-design as it was unnecessary for the known components and unfeasible based on ethical concerns (as evidenced by HalfLytely Summary Basis of Approval Medical Review, in which both institutional review boards and practicing gastroenterologists refused a proposed 4-way component design study because 20 mg bisacodyl alone “is knowingly ineffective for bowel preparation”). The final Phase 3 protocols were Agency approved without factorial design.

**On 5 January 2011**, the Sponsor received comments from the Agency for a protocol amendment and statistical analysis plan sent for review in April/May 2010. These comments were received after the database had been locked. In response to the Agency comments, the Sponsor added to the NDA submission subgroup analyses and added another Intent-to-Treat (ITT) dataset of All Randomized Subjects that included subjects who were not treated.

Other Agency comments dealt with the comparator agent used in the trials, which was the approved branded market leader at the time of the IND filing, as well as the 9% non-inferiority margin, which was previously agreed upon with the Agency.

**On 21 March 2011**, the Sponsor had a Type B, Pre-NDA meeting with the Agency to discuss the content of the PICOPREP NDA submission. The Sponsor communicated its intent to request Priority Review for this NDA. The Sponsor also clarified its understanding that class labeling, related to cardiac risk secondary to electrolyte imbalance, would be included in the labeling. The Sponsor discussed a request for deferral of pediatric assessment.

The Sponsor also agreed to evaluate the human pharmacokinetic profile of sodium picosulfate. The study was undertaken in May 2011 and the results are included in this application.

## **2.6 Other Relevant Background Information**

A Citizen Petition was submitted shortly after the receipt of the NDA. The Petitioner requests the FDA(1) refrain from approving any NDA containing as its active ingredients sodium picosulfate 10 mg, magnesium oxide 3.5 g and citric acid 12 g for bowel cleansing, or (2) if approval of any such sodium picosulfate NDA is granted, that the labeling for such product or a similar formulation be required to carry a boxed warning under 21 C.F.R. 201.57(c)(1) describing the heightened risks of electrolyte imbalance and ischemic colitis posed by sodium picosulfate in this fixed combination product. The petition is currently under review by the Office of Regulatory Policy and the Division of Gastroenterology and Inborn Errors Products.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The following sites were identified for inspection. Site 101, investigator Dr. Gerald Bettinger, MD was chosen because this site had the largest patient enrollment with more successful outcomes than the other sites for Study FE 2009-01 Split Dose Dosing.

Site 106, investigator John Lowe, MD was chosen because Dr. Lowe is the same investigator for Site 212 in Study FE2009-02 Trial Code: 2009-02 FE2009-02 (Day-Before Dosing) “*A Randomized, Assessor-Blinded, Multi- Center Study Investigating the Efficacy, Safety and Tolerability of Day-Before dose PICOPREP for Oral Administration versus HalfLytely for Colon Cleansing in Preparation for Colonoscopy.*”

These two clinical trials were conducted independently of each other. The treatment and care and the investigator response should be independent of other investigators. Participating in both studies may introduce undue bias on the investigator’s part. Information derived from one study may affect the investigator’s ability to remain unbiased in the second study. The drug product used in both studies and the indication for said product use is the same; however, the dosing instructions are different. Ultimately, investigator participation in both studies may influence the results of the studies.

Site 107, investigator Arthur Poch, MD was chosen because he is the same investigator for Site# 212 in Study FE2009-02 (Day-Before Dosing). The rationale for the inspection is the same as stated under Site 106.

Sites 101 and 107 were inspected and Determined NAI per Dr. Khairy Malek. Information regarding Site 106 is pending.

### **3.2 Compliance with Good Clinical Practices**

According to the Applicant, all of the studies were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

### **3.3 Financial Disclosures**

For studies FE 2009-01, and FE 2009-02 the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement 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).

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

There are no significant efficacy or safety issues related to the review of this product.

### **4.2 Clinical Microbiology**

Clinical Microbiology considerations do not apply to this application, because it is not intended as an antimicrobial product.

### **4.3 Preclinical Pharmacology/Toxicology**

The Non clinical reviewer has stated there are no significant efficacy or safety issues related to the review of this product.

### **4.4 Clinical Pharmacology**

The Clinical pharmacology reviewer has stated there are no significant efficacy or safety issues related to the review of this product.

#### **4.4.1 Mechanism of Action**

The active drug substances in each pouch of PICOPREP are sodium picosulfate (10mg), a stimulant cathartic, plus magnesium oxide (3.5g) and citric acid (12.0g) which upon mixing with water, form magnesium citrate, an osmotic laxative.

The activity of these therapeutically active components is well established. Sodium picosulfate (4,4'-[2-pyridylmethylene] diphenyl bis[hydrogen sulfate] disodium salt), as a stimulant cathartic, acts on the nerve endings in the colon to induce peristalsis. This purgative effect, however, is exerted only after hydrolysis of picosulfate, by colonic bacteria, to the active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane (BHPM). Sodium picosulfate is reported to take between 6 and 10 hours to exert its full effect.

Magnesium citrate, as an osmotic laxative, acts in both the small and large intestine to increase the bulk of the intestinal contents by causing the retention of water within the intestinal lumen. A possible additional action on cholecystokinin, which may increase intestinal fluid and electrolyte accumulation, has been reported. Magnesium citrate has

a rapid effect, producing a semi-liquid stool in approximately 3 hours. Thus, the combination of these 2 therapeutically active components produces an efficient dual-action cleansing effect, enabling enhanced visibility for colonoscopy without mucosal harm.

#### **4.4.2 Pharmacodynamics**

The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a dual-action purgative effect which, when ingested with additional fluids, produces watery diarrhea.

#### **4.4.3 Pharmacokinetics**

Sodium picosulfate, which is a prodrug, is converted to its active metabolite, BHPM, by colonic bacteria. After administration of 2 pouches of PICOPREP separated by 6 hours, in 16 healthy volunteers, picosulfate reached a mean  $C_{max}$  of 3.2 ng/mL at approximately 7 hours ( $T_{max}$ ). After the first pouch the corresponding values were 2.3 ng/mL at 2 hours. The terminal half-life of picosulfate was 7.4 hours. The fraction of the absorbed sodium picosulfate dose excreted unchanged in urine is 0.11%. Plasma levels of the free phenol BHPM were consistently low and urinary samples show that the majority of excreted BHPM was the glucuronide-conjugated form. Magnesium oxide and citric acid react to create magnesium citrate, which is only minimally absorbed from the gastrointestinal tract. Peak raw magnesium concentration ( $C_{max}$ ) was approximately 1.9 mEq/L and occurred at 10 hours post initial pouch administration ( $T_{max}$ ).

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

#### Clinical Trials

	Primary Endpoint	Treatment Arms	# of Pts Treated	# of Pts Completing Study
Study FE2009-01 Split Dose Dosing	The proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent or Good according to the Aronchick Scale at Visit 3 during colonoscopy.	PICOPREP	305/608	304 (99%)
		HalfLYTELY	298/608	295 (99%)
Study FE2009-02 Day Before Dosing	The proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent or Good according to the Aronchick Scale <sup>14</sup> at Visit 3 during colonoscopy	PICOPREP	296/598	287 (97%)
		HalfLYTELY	302/598	295 (98%)

## 5.2 Review Strategy

For this NDA submission, Studies FE2009-01 and FE2009-02 were reviewed in detail and the results are discussed in this document. A Citizen Petition was submitted shortly after the receipt of the NDA.

The Petitioner requests the FDA (1) refrain from approving any NDA containing as its active ingredients sodium picosulfate 10 mg, magnesium oxide 3.5 g and citric acid 12 g for bowel cleansing, or (2) if approval of any such sodium picosulfate NDA is granted, that the labeling for such product or a similar formulation be required to carry a boxed warning under 21 C.F.R. 201.57(c)(1) describing the heightened risks of electrolyte imbalance and ischemic colitis posed by sodium picosulfate in this fixed combination product.

After review team discussions an information request (IR) was sent to the applicant on January 19, 2012 for the following information to help inform the responses to the Citizen's Petition:

1) Provide evidence from available data (e.g., the scientific literature) that each component of PICOPREP bowel prep, i.e., sodium picosulfate 10 mg and magnesium oxide 3.5 mg plus citric acid 12 g (combined to form magnesium citrate in solution) makes a contribution to the effect of the product and the dosage of each component.

For this analysis, provide data in tabular form presenting the estimated effectiveness of sodium picosulfate and magnesium citrate (individually) as bowel prep agents, compared against each other as well as the combination product PICOPREP, using the primary endpoint for analysis (success vs. failure using the Aronchick scale) and the secondary endpoint (using the Ottawa scale).

2) Discuss the potential for bisacodyl and sodium picosulfate (individually) to result in colonic mucosal aberrations (e.g., aphthous ulcers) or precipitate ischemic colitis. Provide an overview of pre- and post-market data regarding the frequency of ischemic colitis, rectal bleeding, intestinal bleeding, or gastrointestinal bleeding with the use of the PICOPREP product. A response referring us to the already submitted datasets or postmarketing safety update reports (PSURs) would be unacceptable.

3) Provide a tabulation of known cases of electrolyte imbalances or derangements that occurred in patients who have used PICOPREP and were associated with any of the following: dehydration, syncope, loss of consciousness, seizures, and cardiac arrhythmias

4) Provide any case reports of flares of inflammatory bowel disease (IBD), specifically ulcerative colitis and Crohn's disease, associated with the use of PICOPREP.

A thorough review of the literature was conducted to provide information for response pertinent to the Citizen's petition and the review of this document.

The applicant was also asked to perform a TQT study, or submit a request for a waiver of the requirement for a TQT study with adequate justification (based in part on human PK data) for FDA to review.

### **5.3 Discussion of Individual Studies/Clinical Trials**

#### **Study FE2009-01 Split- Dose Dosing**

Study FE2009-01 was a phase 3 randomized, assessor blinded, multi-center study investigating the efficacy, safety and tolerability of "split dose" PICOPREP™ for Oral administration versus HalfLyte® for colon cleansing in preparation for colonoscopy in adult subjects. The study was conducted at 10 investigative sites in the United States

#### **Study Period**

10 May 2010 to 12 October 2010.

#### **Study Objectives**

Primary Objective: To demonstrate non-inferiority of PICOPREP to HalfLyte in overall colon cleansing in preparation for colonoscopy.

Secondary Objectives:

- 1) To demonstrate the efficacy of ascending colon cleansing in a non-inferiority fashion.
- 2) To determine tolerability and satisfaction of the preparation as assessed by a standardized subject questionnaire administered at the study site before colonoscopy.
- 3) To evaluate the safety and tolerability through the collection of adverse events, clinical laboratory tests, and physical examination.

#### **Study Design**

Subjects requiring an elective complete colonoscopy were screened for inclusion in the study at Visit 1.

Those subjects who fulfilled all inclusion and no exclusion criteria were randomly assigned to 1 of the 2 preparations (PICOPREP or HalfLyte). At Visit 2: Subjects randomized to the PICOPREP treatment group were instructed to begin taking treatment (first reconstituted pouch) between 5:00 PM and 9:00 PM on the day before colonoscopy (in the evening before Visit 3) and to complete taking treatment (second reconstituted pouch) the next day (the day of the colonoscopy, Visit 3) at least 5 hours prior to but no later than 9 hours prior to colonoscopy.

Following the first administration of PICOPREP, subjects were to consume five 8-ounce glasses of clear liquids over the next few hours and following the second administration

of PICOPREP, subjects were to consume three 8-ounce glasses of clear liquids before the colonoscopy.

Subjects randomized to the HalfLyte treatment group were instructed to begin their treatment (following the approved label instructions) by taking two 5 mg bisacodyl tablets in the afternoon on the day before colonoscopy, and then after the first bowel movement or after 6 hours, whichever occurred first, to drink the 2 L of HalfLyte solution at a rate of one 8-ounce glass every 10 minutes. The HalfLyte treatment group completed treatment on the day before colonoscopy.

Only the site's designated unblinded coordinator knew the subject's randomized treatment group. The unblinded coordinator instructed the subject on the use of the bowel preparation and gave the subject a diary card that provided dosing instructions and space to record whether the subject completed dosing requirements. On the day before the procedure (24 hours before), all subjects were limited to a clear liquid diet only. All assessments were performed at Visit 3 (day of colonoscopy). Prior to the colonoscopy, subjects completed an Acceptability and Tolerability Questionnaire. During the colonoscopy, the blinded assessor evaluated overall colon cleanliness using the Aronchick Scale and cleanliness of the ascending colon, mid colon, and recto-sigmoid colon using the Ottawa Scale; a fluid assessment was also performed. The studies consisted of 6 visits, including Screening (Visit 1), day of randomization (Visit 2), day of colonoscopy (Visit 3), and 3 follow-up visits: within 24 to 48 hours (Visit 4), in 7 days (Visit 5), and in 4 weeks (Visit 6) after the colonoscopy procedure. All efficacy assessments were performed at Visit 3, the day of the colonoscopy.

Safety was evaluated by collection of adverse events, physical examinations, vital signs, clinical laboratory tests, and electrocardiograms (ECGs). Investigators monitored subjects for clinical and laboratory evidence of adverse events throughout the studies. Abdominal bloating, distension, pain/cramping, and watery diarrhea were clinical changes that, if noted by the subject, were not to have been documented as adverse events, unless the findings induced an action (e.g., led the study discontinuation). Physical examinations were conducted and vital signs (orthostatic blood pressure and pulse rate) were collected at each visit (i.e., Visits 1 through 6). Samples for laboratory determinations (hematology, coagulation, chemistry, urinalysis) were collected and 12-lead ECGs were performed at Visits 1, 3, 4, 5, and 6.

A total of 608 subjects were randomized, 5 of whom were not treated. Of the 603 treated patients, 305 subjects received PICOPREP and 298 subjects received HalfLyte. Of these, 304 (99%) PICOPREP subjects and 295 (99%) HalfLyte subjects completed the study.

## **Study Population**

### **Selection of Trial Population for Study FE2009-01 (Split-Dose Dosing) and Study FE2009-02 (Day-Before Dosing)**

Subjects who were candidates for participation in the study were screened for inclusion/exclusion criteria before enrollment into the study. The subject's eligibility was documented in the CRF. Screening evaluations were to be conducted within 21 days prior to study enrollment and randomization.

### **Inclusion Criteria**

For inclusion in the study, patients had to meet all of the following criteria at screening and baseline:

1. Male or female aged 18 to 80 years, inclusive, scheduled to undergo elective colonoscopy.
2. Female subjects must have been postmenopausal ( $\geq 45$  years with no menstrual period for at least 12 months without an alternative medical cause), surgically sterile, or using medically approved contraception throughout the study period.
3. Females of childbearing potential must have had a negative pregnancy test at screening and again at randomization.
4. Subjects must have had at least 3 spontaneous bowel movements per week for 1 month prior to the colonoscopy.
5. Subjects must have been willing, able, and competent to complete the entire procedure and to comply with study instructions.
6. Subjects must have signed written informed consent at screening.

### **Exclusion Criteria**

Patients were excluded from the study if they met any of the criteria at screening or baseline:

1. Acute surgical abdominal conditions (e.g., acute obstruction or perforation).
2. Active (acute/exacerbation of/severe/uncontrolled) inflammatory bowel disease (IBD).
3. Any prior colorectal surgery, excluding appendectomy, hemorrhoid surgery, or prior endoscopic procedures.

4. Colon disease (toxic megacolon, toxic colitis, idiopathic pseudo-obstruction, hypomotility syndrome)
5. Ascites
6. Gastrointestinal (GI) disorder (active ulcer, outlet obstruction, retention, gastroparesis, ileus).
7. Upper GI surgery (gastric resection, gastric banding, gastric bypass).
8. Uncontrolled angina and/or myocardial infarction (MI) within last 3 months, congestive heart failure, or uncontrolled hypertension.
9. Renal insufficiency (serum creatinine and potassium must be within normal limits).
10. Participation in an investigational study within 30 days prior to receiving study treatment (or within 60 days for participation in an investigational study using drugs with an elimination half-life >15 days).
11. Any clinically significant laboratory value at the screening, including pre-existing electrolyte abnormality, based on clinical history, if, in the opinion of the Investigator, this may affect the study evaluation.
12. Hypersensitivity to active ingredients.

***Reviewer Comment: The inclusion and exclusion criteria appear appropriate for the study.***

#### **Study FE2009-02 Day Before Dosing**

Study FE2009-02 was a phase 3 randomized, assessor blinded, multi-center study investigating the efficacy, safety and tolerability of “day before” PICOPREP™ for oral administration versus HalfLytely® for colon cleansing in preparation for colonoscopy in adult subjects. The study was conducted at 12 investigative sites in the United States

#### **Study Period**

10 May 2010 to 18 October 2010

#### **Study Objectives**

The study objectives for Study FE2009-02 Day Before Dosing are identical to those for Study FE2009-01 Split Dose Dosing. Please see the primary and secondary objectives previously discussed above.

## **Study Design**

Subjects requiring an elective complete colonoscopy were screened for inclusion in the study at Visit 1.

Those subjects who fulfilled all inclusion and no exclusion criteria were randomly assigned to 1 of the 2 preparations (PICOPREP or HalfLyte). At Visit 2 to be completed on the day before the colonoscopy: Subjects randomized to the PICOPREP treatment group were instructed to begin taking treatment (first reconstituted pouch) between 4:00 PM and 6:00 PM one day before colonoscopy (in the afternoon before Visit 3) and to complete taking treatment (second reconstituted pouch) at least 6 hours later, between 10:00PM and 12:00AM. Following the first administration of PICOPREP, subjects were to consume five 8-ounce glasses of clear liquids of their choice in the late afternoon and following the second administration of PICOPREP on the night before the colonoscopy, subjects were to consume three 8-ounce glasses of clear liquids of their choice.

Subjects randomized to the HalfLyte treatment group were instructed to begin their treatment (following the approved label instructions) by taking two 5 mg bisacodyl tablets in the afternoon on the day before colonoscopy, and then after the first bowel movement or after 6 hours, whichever occurred first, to drink the 2 L of HalfLyte solution at a rate of one 8-ounce glass every 10 minutes. The HalfLyte treatment group completed treatment on the day before colonoscopy.

Only the site's designated unblinded coordinator knew the subject's randomized treatment group. The unblinded coordinator instructed the subject on the use of the bowel preparation and gave the subject a diary card that provided dosing instructions and space to record whether the subject completed dosing requirements. On the day before the procedure (24 hours before), all subjects were limited to a clear liquid diet only. All assessments were performed at Visit 3 (day of colonoscopy). Prior to the colonoscopy, subjects completed an Acceptability and Tolerability Questionnaire. During the colonoscopy, the blinded assessor evaluated overall colon cleanliness using the Aronchick Scale and cleanliness of the ascending colon, mid colon, and recto-sigmoid colon using the Ottawa Scale; a fluid assessment was also performed. The studies consisted of 6 visits, including Screening (Visit 1), day of randomization (Visit 2), day of colonoscopy (Visit 3), and 3 follow-up visits: within 24 to 48 hours (Visit 4), in 7 days (Visit 5), and in 4 weeks (Visit 6) after the colonoscopy procedure. All efficacy assessments were performed at Visit 3, the day of the colonoscopy.

Safety was assessed for Study FE2009-02 Day Before Dosing as it was for Study FE2009-01 Split Dose Dosing. Safety was evaluated by collection of adverse events, physical examinations, vital signs, clinical laboratory tests, and electrocardiograms (ECGs). Investigators monitored subjects for clinical and laboratory evidence of adverse events throughout the studies. Abdominal bloating, distension, pain/cramping, and

watery diarrhea were clinical changes that, if noted by the subject, were not to have been documented as adverse events, unless the findings induced an action (e.g., led to study discontinuation). Physical examinations were conducted and vital signs (orthostatic blood pressure and pulse rate) were collected at each visit (i.e., Visits 1 through 6). Samples for laboratory determinations (hematology, coagulation, chemistry, and urinalysis) were collected and 12-lead ECGs were performed at Visits 1, 3, 4, 5, and 6.

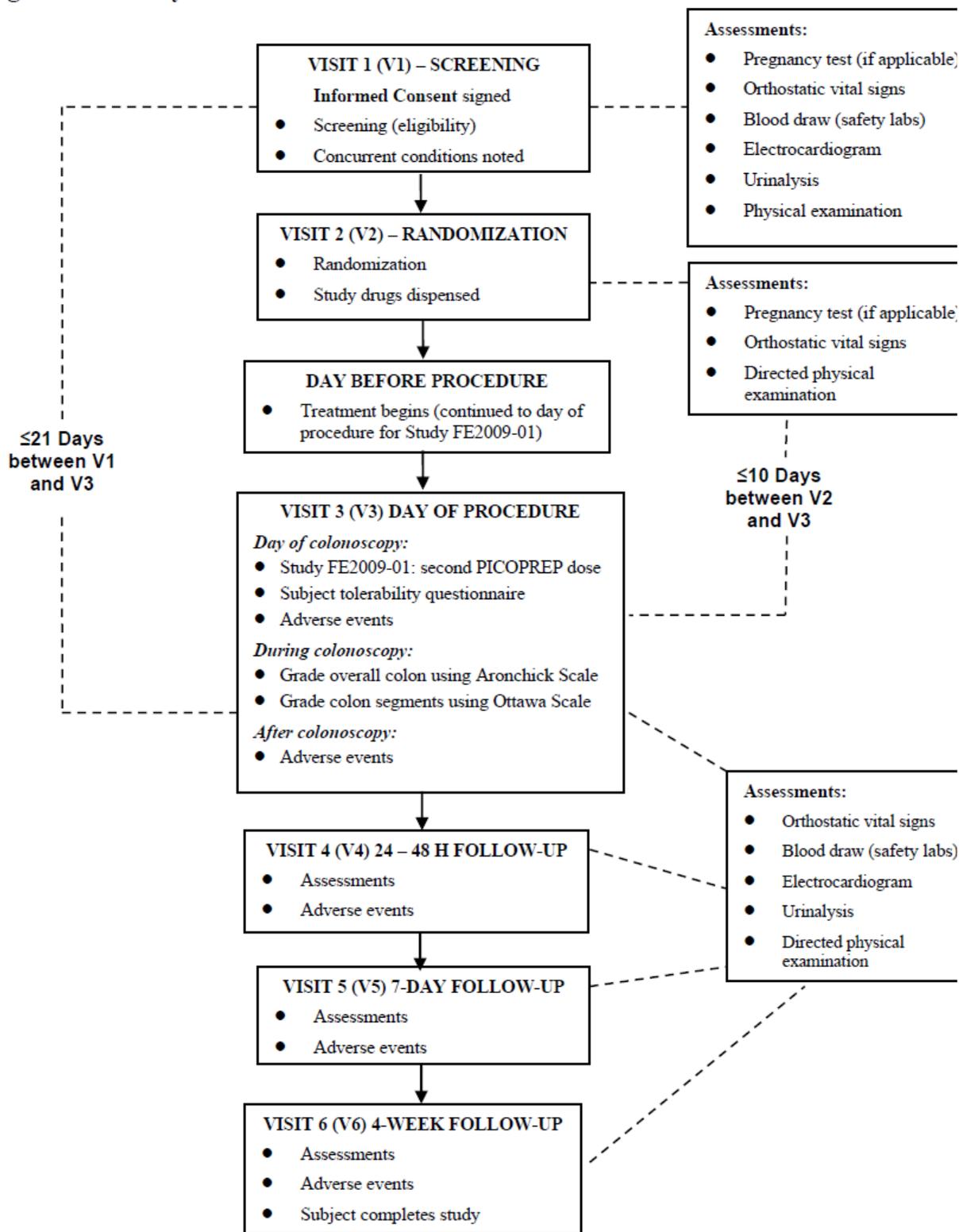
A total of 603 subjects were randomized, 5 of whom were not treated. Of the 598 treated subjects; 296 subjects received PICOPREP and 302 subjects received HalfLytely. Of these, 287 (97.0%) PICOPREP subjects and 295 (97.7%) HalfLytely subjects completed the study.

### **Study Procedures**

Study FE2009-01 is the primary study establishing efficacy for the Split-Dose dosing regimen. Study FE2009-02 is the primary study establishing efficacy for the Day-Before dosing regimen.

A study flow chart for Studies FE2009-01 and FE2009-02 is presented in the figure below.

**Figure 1 Study Flow Chart for Studies FE2009-01 and FE2009-02**



### **Clinical Evaluations**

#### Medical History and demographic data

A thorough medical history and demographic data (age, sex, and race) were obtained at Visit 1.

#### Physical Examination

A complete physical examination was conducted at the investigational site at Visit 1. At Visits 2 through 6, a directed physical examination was performed. Height and weight were measured at Visit 1 only.

After study drug administration, any new abnormal findings or worsening of an ongoing abnormal condition were to be recorded as an adverse event.

#### Vital Signs

Orthostatic vital signs (supine and standing blood pressure and pulse) were measured at Visits 1 through 6.

#### Electrocardiogram (ECG)

Electrocardiogram (12-lead) measurements were obtained at Visit 1 and at Visits 3 through 6. All ECG data were transferred electronically to, and centrally read by, ERT (Philadelphia, PA), an expert cardiac safety assessment facility. Trained analysts, who were blinded to study treatment, reviewed all ECGs for correct lead and beat selection and adjudicated the preplaced algorithm calipers as necessary using a proprietary validated electronic caliper system applied on a computer screen (manual adjudication methodology).

For all ECGs, both raw and corrected interval measurements were then analyzed by a cardiologist for central tendency, outliers, and morphology.

The following values were reported:

- Ventricular rate (beats/min)
- PR interval (msec)
- QRS (msec)
- QT interval (msec)
- QTc interval (msec)

#### Concomitant Medication Assessment

Concomitant medications were reported and recorded at Visit 1 and at Visits 3 through 6.

Medications were coded using the World Health Organization Drug Coding Dictionary (WHO-DRUG), version 2010, March 01.

### Clinical Laboratory Variables

All laboratory measurements were performed using appropriately validated methods by (b) (4). Investigators assessed all out-of-range values as either clinically significant or not clinically significant. Clinically significant out-of-range laboratory values may have been considered AEs as evaluated by the local Investigator.

Following Visit 1, subjects with clinically significant abnormal laboratory values were not randomized into this study.

Samples were collected during both Visit 1 and Visits 3 through 6 for determination of the following test values:

- Hematology panel:  
Full complete blood count (CBC) and differential
- Coagulation panel:  
Prothrombin time (PT), activated partial thromboplastin time (aPTT)
- Full chemistry panel:  
Calculated creatinine clearance  
Serum magnesium (Mg++)  
Serum chemistry: glucose, blood urea nitrogen (BUN), potassium, sodium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT)

#### Urinalysis panel

Urine pregnancy tests were performed at the local laboratory for premenopausal subjects at Visits 1 and 2.

**Reviewer Comment: Since this product has not been approved in the United States, a thorough QTc study was recommended by the Agency, if picosulfate was greater than minimally bioavailable.**

**The applicant asserted sodium picosulfate is a locally acting, stimulant cathartic of the triarylmethane class, with a mode of action similar to bisacodyl. Picosulfate is a prodrug, like bisacodyl, with no known pharmacologic activity of its own. In addition, this chemical and pharmacologic class has not been associated with QT/QTc interval prolongation or Torsades de Pointes ventricular tachycardia based on considerable post-marketing surveillance. In keeping with the request, however, the Sponsor agreed to include extensive ECG data collection throughout the Phase 3 studies.**

**The ECG measurements were determined using standard methods by a central ECG laboratory, consistent with Food and Drug Administration (FDA) Guidance.**

**A quality-control review process was used, and central ECG laboratory cardiologists reviewed 100% of all ECGs. Cardiologists made interpretations of morphology and other parameters.**

**In a request for information RFI sent January 19,2012, the Applicant was asked to perform a TQT study, or submit a request for a waiver of the requirement for a TQT study with adequate justification (based in part on human PK data) for FDA to review. At this time neither the waiver nor the thorough QT study have been submitted.**

## **6 Review of Efficacy**

### **Efficacy Summary**

#### **6.1 Indication**

Both Study FE2009-01 and Study FE2009-02 were Phase 3, randomized, multicenter, assessor-blinded, parallel-group, active-control, non-inferiority studies investigating the efficacy, safety, and tolerability of PICOPREP versus the currently approved HalfLytely for colon cleansing in preparation for colonoscopy in adult subjects.

##### **6.1.1 Methods**

There were 3 analysis sets in this study: the Intent-to-treat (ITT) analysis data set, the Per-Protocol (PP) analysis set, and the Safety analysis set. All randomized subjects who received any study drug were included in 1 or more of the analysis data sets with no imputation for missing values.

###### **1. Intent-to-treat Analysis Set (Full Analysis Set)**

All randomized subjects who received any study treatment and produced efficacy assessment data (Aronchick Scale and/or Ottawa Scale) were included in the ITT analysis data set.

###### **2. Per-Protocol Analysis Set**

Subjects who had major protocol violations, including not taking study drug in the prescribed time intervals, were excluded from the PP analysis set. Subjects to be excluded from the PP analysis set were identified prior to breaking the study blind. Treatment assignment for summary and analysis was according to randomization.

### 3. Safety Analysis Set

All subjects who received any study treatment were included in the Safety analysis data set.

Treatment assignment for summary and analysis was based on actual treatment. The primary endpoint analyses (the proportion of responders based on the Aronchick Scale) were performed on the All Randomized Subjects analysis set.

The Food and Drug Administration (FDA) “Guidance for Industry: Non-Inferiority Clinical Trials” was used as guidance for the development of the statistical methodology for this study.

Non-inferiority studies seek to show that the difference in response between the active control and the test drug, the amount by which the control is superior to test drug, is less than some prespecified NI margin (M2).

Although the NI margin used in a trial can be no larger than the entire assumed effect of the active control in the NI study (M1), it is usual and generally desirable to choose a smaller value, called M2, for the NI margin. The intent of this study was to demonstrate NI of PICOPREP to HalfLytely for overall colon cleansing prior to colonoscopy, as assessed by a blinded colonoscopist using the Aronchick scale.

A subject was considered a responder/success if overall colon cleansing was either “excellent” or “good” on the Aronchick 4-point scale. The active comparator for this study, HalfLytely (two 5 mg bisacodyl tablets plus 2 L PEG-EL), was chosen because it has been shown to be effective and was the most commonly used colon cleansing preparation in the US at the time of study initiation.

Historical references were used to construct the anticipated responder rate of 85%. Based on the similarity of the current trial design to the historical studies, there was a considerable likelihood that the current effect of the active control would be similar to the past (constancy assumption).

To determine the entire effect of the active control assumed to be present in this study (M1), the anticipated placebo response rate of 15% (range 0% to 15%) was used, based on Statistical Review and Evaluation of the HalfLytely 20 mg/2 L Tablets. This estimates the M1 component of the current study to be 70% (85% to 15%).

The sample size was determined assuming an estimated responder rate of 85% for both the PICOPREP-treated and HalfLytely-treated subjects, a 9.0% NI margin, 85% power, and a 1-sided significance level of 0.025. Based on these assumptions, and using StatXact, Version 6.2, Cytel Software Corp., it was determined that 287 subjects were required for each treatment group. To allow for departure from these assumptions, a total of 600 subjects (~300 for each treatment group) was planned to be enrolled into this study.

## Efficacy Assessments For Studies FE2009-01 (Split- Dose Dosing) and FE2009-02 (Day- Before Dosing)

### Primary Endpoint

The blinded colonoscopist performed the primary efficacy assessment of overall colon cleansing, using the Aronchick Scale. The Aronchick Scale is universally accepted and has been used in other pivotal trials including the approval of HalfLytely. Cleanliness was reported by describing the overall preparation of the colon, assigning a grade of excellent, good, fair, or inadequate, according to the definitions given in the table below. For the purpose of analysis, a subject was considered a responder following administration of the preparation if overall colon cleansing was rated as excellent or good on this 4-point scale. The colonoscopist also recorded in the CRF whether the colonoscopy was completed. If the colonoscopy was not completed, the reason and whether a repeat procedure was required were to be recorded.

Table 1 Aronchick Scale

Grade	Description
Excellent	>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization
Good	>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	<90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

Source: Table 5-2. CSR FE2009-02,p.26/81.

The scale was evaluated as:

Responder: grade of excellent or good

Not a Responder: grade of fair or inadequate

### Secondary endpoints

The blinded colonoscopist performed the key secondary efficacy assessment of ascending colon cleansing, using the Ottawa Scale. Cleanliness was reported by assigning a score of 0, 1, 2, 3, or 4 according to the definitions in the table below.

For the purpose of analysis, a subject was considered a clinical success following the preparation, if ascending colon cleansing was scored 0, 1, or 2 (excellent, good, or fair) on this 5-point scale. In addition, cleanliness of both the mid (transverse,descending) colon and the descending (recto-sigmoid) colon was evaluated using the Ottawa Scale.

If the colonoscopist was unable to reach any of the ascending, transverse, or descending segments due to poor quality bowel preparation, that segment was automatically assigned a “4”. Overall fluid amount, graded on a scale from 0 to 2, was also reported by the colonoscopist. The fluid score scale was 0 (small), 1 (medium), or 2 (large).

To further describe the cleansing effect of the preparation, the Total Ottawa Scale score was determined in this study and ranged from 0 (the best) to 14 (the worst). This total score was determined by adding the 0- to 4-point score for each of the 3 colon segments, then adding the overall fluid assessment score (from 0 to 2).

Thus, the best score for a preparation would be 0 (all 3 segments excellent = 0 and fluid level small = 0) and the worst score would be 14 (all segments inadequate and fluid amount large = (4 + 4 + 4 + 2).

The Ottawa Scale is a validated scale for the assessment of bowel preparation quality and it demonstrated high inter-observer agreement and reliability.

Table 2 Ottawa Scale

Grade	Description
0	Excellent: Mucosal detail clearly visible. If fluid is present, it is clear. Almost no stool residue.
1	Good: Some turbid fluid or stool residue but mucosal detail visible. Washing and suctioning not necessary.
2	Fair: Turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary.
3	Poor: Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained.
4	Inadequate: Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

Source: Table 5-3. CSR FE2009-02,p.27/81.

### **Subject Tolerability and Satisfaction Questionnaire**

A standard questionnaire was used to assess subject’s tolerability and satisfaction and compared the treatment groups. This questionnaire was administered to subjects by the study site coordinator at Visit 3 prior to any preliminary sedation for the colonoscopy.

The questions were listed in no order of importance:

1. How easy or difficult was it to consume the study drug?
2. Were you able to consume the entire prep as instructed?

3. Please describe your overall experience of the study preparation:
4. The taste of this study preparation was:
5. Would you ask your doctor for this preparation again if you need another colonoscopy in the future?
6. Would you refuse the same preparation again if it were to be prescribed to you in the future?
7. Have you had a colonoscopy before (within the past 3 years)?
  - 7a. If yes, which type of colon cleansing medication(s) did you receive?
  - 7b. If yes, provide the name of the colon cleansing medication used in most recent colonoscopy
  - 7c. If yes, do you remember if you were able to complete as instructed the entire colon cleansing medication you used in your most recent colonoscopy?
  - 7d. If yes, would you describe the colon cleansing medications you received for this colonoscopy as? (1: Much better --- 5: Much worse)

**Reviewer Comment: The Aronchick and Ottawa scales are instruments used in clinical trials to assess bowel preparation quality. The Ottawa scale is particularly useful because it assess each colonic segment separately. This is important in determining how well a product performs in the ascending colon. It is estimated that up to 30% of missed adenomas are located in the right colon. Because adenomas may develop into malignant lesions, a product that performs well in cleansing the right colon for adequate visualization of the mucosa is essential for effective colon cancer screening. The patient tolerability scale is subjective and its usefulness would probably inform marketing decisions rather than labeling.**

## 6.1.2 Demographics

### Demographic and Other Baseline Characteristics

The study population consisted of adults who were undergoing diagnostic or therapeutic colonoscopy in a natural endoscopic practice setting and met the inclusion/exclusion criteria. No statistically significant differences were observed between treatment groups in any demographic characteristic in the Safety, ITT, and PP analysis sets.

**Study FE2009-01 (Split-dosing)**

In the safety analysis set, the majority of the population was female (59%), White (88%), and <65 years of age (83%). Subjects ranged in age from 19 to 80 years, with a median age of 55 years. Demographic characteristics of the IITT and PP analysis sets were similar to those of the Safety analysis set.

Table 3 Demographic and Baseline Characteristics (Safety Analysis Set) (FE2009-01)

Demographic Characteristic	TREATMENT GROUP			p-value
	PICOPREP N= 305	HalfLyte N= 298	Total N= 603	
Age (years) Median Range	55 22-77	56 19-80	55 19-80	0.3115
Age ≥ 65 N (%)	52 (17)	48 (16)	100 (17)	
Sex, n (%) Male Female	124 (41) 181 (59)	124 (42) 174 (58)	248 (41) 355 (59)	0.8686
Race, n (%) White Black	265 (87) 36 (12)	268 (90) 27 (9)	533 (88.4) 63 (10)	
Height (cm) Median	168	168	168	0.8485
Weight (kg) Median	83	84	83	0.8007
BMI (kg/m <sup>2</sup> ) Median	29	29	29	0.8021

Source: Adapted from Sponsor's Table 7-4, CSR FE2009-01, p.45/80.

**Medical History**

Medical history is presented for the Safety analysis set by SOC. The proportions of subjects reporting medical histories by various body systems were generally similar between the PICOPREP and HalfLyte treatment groups. The majority of the subjects in both treatment groups reported medical histories at baseline (PICOPREP 99.3% and HalfLyte 98%). The most commonly reported medical histories were those related to

GI (PICOPREP 77% and HalfLyte 73%); Renal/genitourological (PICOPREP 65% and HalfLyte 61%); cardiovascular (PICOPREP 57% and HalfLyte 56%); musculoskeletal (PICOPREP 54% and HalfLyte 55%).

At baseline none of the subjects in either treatment group had abnormal clinically significant findings on physical examination.

### Prior and Concomitant Medications

Prior to the start of the study, 14% of subjects in the PICOPREP group and 12% of subjects in the HalfLyte group took at least 1 medication. The most commonly reported medications that were taken included iron, polyethylene glycol, acetylsalicylic acid, and hydrocodone/acetaminophen.

All subjects took at least 1 concomitant medication. The most commonly reported medications taken after the start of the study drug dosing were sedative and analgesic drugs routinely administered for the colonoscopy procedure. Concomitant medications taken by ≥10% of subjects in either treatment group are presented in the table below.

Table 4 Concomitant Medications Taken by ≥10% of Subjects in Either Treatment Group (Safety Analysis Set) FE2009-01

MEDICATION	PICOPREP (N=305) N (%)	HalfLyte (N=298) n(%)	Total (N=603) N (%)
Subjects w/≥1 concomitant med	305 (100)	298 (100)	603 (100)
Propofol	206 (68)	188 (63)	394 (65)
Fentanyl	81 (27)	101 (34)	182 (30)
Midazolam HCl	73 (24)	98 (33)	171 (28)
Lidocaine	71 (23)	71 (24)	142 (24)
Multivitamins	71 (23)	63 (21)	134 (22)
ASA	71 (23)	60 (20)	131 (22)
Pethidine	52 (17)	43 (14)	95 (16)
Simvastatin	39 (13)	37 (12)	76 (13)
Fish oil	35 (12)	33 (11)	68 (11)
Ibuprofen	33 (11)	31 (10)	64 (11)
Calcium	33 (11)	29 (10)	62 (10)
Lisinopril	24 (8)	31 (10)	55 (9)
Vitamin D	33 (11)	21 (7)	54 (9)
Levothyroxine sodium	31 (10)	21 (7)	52 (9)

Source: Adapted from Sponsor's Table 7-5, CSR FE2009-01, p.46/80

**Reviewer Comment: The most common concomitant medications were those taken for sedation prior to colonoscopy. Medications that may increase the risk for fluid and electrolyte disturbances such as angiotensin converting enzymes, angiotensin receptor blockers, diuretics, and non steroidal anti inflammatory drugs do not appear to have been used in abundance.**

**Study FE2009-02 (Day Before dosing)**

In the safety analysis set, the majority of the population was female (64%), White (91%), and <65 years of age (81%). Subjects ranged in age from 18 to 79 years, with a median age of 57 years. Demographic characteristics of the ITT and PP analysis sets were similar to those of the Safety analysis set.

A summary of demographic and baseline characteristics of subjects is presented for the Safety analysis set in the Table below.

Table 5 Demographic and Baseline Characteristics (Safety Analysis Set) (FE2009-02)

Demographic Characteristic	TREATMENT GROUP			p-value
	PICOPREP N= 296	HalfLyteLy N= 302	Total N= 598	
Age (years) Median Range	57 21-78	56 18-79	55 18-79	0.5486
Age ≥ 65 N (%)	60 (20)	55 (18)	115 (19)	
Sex, n (%) Male Female	104 (35) 192 (65)	113 (37) 189 (63)	217 (36) 381 (64)	0.6099
Race, n (%) White Black	274 (93) 22 (7.4)	268 (89) 32 (11)	542 (91) 54 (9)	
Height (cm) Median	168	168	168	0.8566
Weight (kg) Median	82	82	82	0.9067
BMI (kg/m <sup>2</sup> ) Median	29	29	29	0.9287

Source: Adapted from Sponsor's Table 7-4, CSR FE2009-02, p.45/81

### **Medical History**

Medical history is presented for the Safety analysis set by SOC. The proportions of subjects reporting medical histories by various body systems were generally similar between the PICOPREP and HalfLyte treatment groups. The majority of the subjects in both treatment groups reported medical histories at baseline (PICOPREP 99% and HalfLyte 99%). The most commonly reported medical histories were those related to GI (PICOPREP 75% and HalfLyte 73%); Renal/genitourological (PICOPREP 62% and HalfLyte 59%); cardiovascular (PICOPREP 59% and HalfLyte 57%); musculoskeletal (PICOPREP 60% and HalfLyte 62%).

At screening 1 subject in each treatment group had an abnormal, clinically significant finding on physical examination; PICOPREP subject had 2+ edema of the right ankle and HalfLyte subject was hemoccult positive.

### **Prior and Concomitant Medications**

Prior to the start of the study, 20% of subjects in the PICOPREP group and 17% of subjects in the HalfLyte group took at least 1 medication. The most commonly reported medications that were taken included acetylsalicylic acid, MVI, fish oil, iron, hydrocodone/acetaminophen, ascorbic acid, ibuprofen, acetaminophen/propoxyphene, calcium, hydrocodone, polyethylene glycol and vitamin D.

All subjects took at least 1 concomitant medication. The most commonly reported medications taken after the start of the study drug dosing were sedative and analgesic drugs routinely administered for the colonoscopy procedure.

Concomitant medications taken by  $\geq 10\%$  of subjects in either treatment group are presented in the table below.

Table 6 Concomitant Medications Taken by ≥10% of Subjects in Either Treatment Group (Safety Analysis Set) FE2009-02

MEDICATION	PICOPREP (N=296) n (%)	HalfLyteLy (N=302) n (%)	Total (N=598) n (%)
Subjects w/≥1 concomitant med	296 (100)	302 (100)	598 (100)
Propofol	207 (70)	213 (70)	420 (70)
Fentanyl	103 (35)	94 (31)	197 (33)
Midazolam HCl	140 (47)	118 (39)	258 (43)
Lidocaine	80 (27)	64 (21)	144 (24)
Multivitamins	68 (23)	61 (20)	129 (22)
ASA	66 (22)	68 (23)	134 (22)
Pethidine	39 (13)	35 (12)	74 (12)
Simvastatin	26 (9)	41 (14)	67 (11)
Fish oil	39 (13)	35 (11)	74 (12)
Ibuprofen	31 (11)	31 (10)	62 (10)
Calcium	31 (11)	33 (11)	64 (11)
Lisinopril	34 (12)	27 (9)	61 (10)
Oxygen	26 (9)	34 (11)	60 (10)
Omeprazole	26 (9)	31 (10)	57 (10)

Source: Adapted from Sponsor's Table 7-5, CSR FE2009-02, p.47/81

**Reviewer Comment: The concomitant medications taken by patients in the Day before dosing group do not differ from those taken by patients in the Split-dosing group. Medications used for sedation for colonoscopy appear as most commonly used. Other medications that may increase the risk for fluid and electrolyte disturbances appear to have been infrequently used.**

### 6.1.3 Subject Disposition

608 subjects were randomized in Study FE2009-01; 8/608 subjects were randomized manually, 6 to PICOPREP and 2 to HalfLyteLy. Five randomized subjects (2 PICOPREP, 3 HalfLyteLy) were not treated and were excluded from all analyses. Therefore a total of 603 subjects were enrolled and treated. 305 subjects were assigned to receive PICOPREP and 298 subjects were assigned to receive HalfLyteLy. 304/305 (99.7%) PICOPREP subjects and 295/298 (99.0%) HalfLyteLy subjects completed the study. Overall, 4 subjects discontinued the study.

- One PICOPREP subject withdrew consent (105-018)

- Three HalfLyteLy subjects prematurely discontinued
  - 1 had an adverse event of nausea (106-092)
  - 1 was withdrawn due to noncompliance (101-112)
  - 1 had an inadequate bowel preparation and colonoscopy could not be performed (104-038)

Table 7 Subject Disposition (FE2009-01)

	TREATMENT GROUP		
	PICOPREP	HalfLyteLy	Total
Total randomized	307	301	608
Not treated	2	3	5
Withdrawal by subject	2	2	4
Lost to follow-up	0	1	1
Total treated	305	298	603
Total completed, n(%)	304 (99.7)	295 (99.0)	599 (99.3)
Total discontinuations, n(%)	1 (0.3)	3 (1.0)	4 (0.7)
Withdrawal by subject	1(0.3)	0	1 (0.2)
Adverse event	0	1 (0.3)	1 (0.2)
Noncompliance with study drug	0	1 (0.3)	1 (0.2)
Other <sup>a</sup>	0	1 (0.3)	1 (0.2)

<sup>a</sup>. Other: HL subject 104-038: inadequate pre, unable to do procedure

Note: Two subjects were identified for whom actual treatment received differed from randomized, planned treatment group assignment:

PicoPrep Subject 110-021 and HalfLyteLy Subject 110-002; these 2 subjects were assessed under the planned group assignment in the ITT analysis set and were excluded from the PP analysis set.

a. Other: HalfLyteLy Subject 104-038: inadequate prep, unable to do procedure

Source: Sponsor's Table 7 -1, CSR FE2009-01, p.41/ 80.

#### Disposition of Subjects for Study FE2009-02 "Day Before" PICOPREP

603 subjects were randomized in Study FE2009-02. 5/603 subjects were randomized manually, 2 to PICOPREP and 3 to HalfLyteLy. Five randomized subjects (4 PICOPREP and 1 HalfLyteLy) were not treated and were excluded from all analyses. Therefore a total of 598 subjects were enrolled and treated; 296 subjects were assigned to receive PICOPREP and 302 subjects were assigned to receive HalfLyteLy. 287/296 (97%) PICOPREP subjects and 295/302 (98%) HalfLyteLy subjects completed the study. 16 subjects discontinued the study.

Clinical Review

Zana H. Marks, MD, MPH

NDA 202535

PICOPREP™ (sodium picosulfate, magnesium oxide and citric acid)

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- 6 subjects withdrew consent ; (PICOPREP Subject 203-048, PICOPREP Subject 204-029, PICOPREP Subject 204-044, PICOPREP Subject 208-007, PICOPREP Subject 212-014, and HalfLyte Subject 204-004);
- 3 subjects discontinued due to protocol deviations; PICOPREP subject 202-042: incomplete scope due to poor quality of prep; PICOPREP subject 212-048: patient could not return to site for visits 4 and 5; HalfLyte subject 211-039: prep did not work
- 2 subjects 204-057 and 210-045 were lost to follow-up; both were in the HalfLyte treatment group
- 3 subjects discontinued for other reasons 1 PICOPREP subject 202-039: Visit 3 colonoscopy could not be performed due to a power outage at the site; 1 HalfLyte subject 207-036 forgot; 1 HalfLyte subject 210-049 was unable to return for Visit 6
- 2 subjects discontinued due to adverse events 1 PICOPREP subject 204-038: vomiting; 1 HalfLyte subject 212-081: vomiting, migraine, dizziness, syncope

Table 8 Subject Disposition (FE 2009-02)

	TREATMENT GROUP		
	PICOPREP	HalfLyte	Total
Total randomized	300	303	603
Not treated (incl. incomplete prep)	4	1	5
Withdrawal by subject	3	1	4
Other: could not tolerate prep	1	0	1
Total treated	296	302	598
Total completed, n (%)	287(97)	295(98)	582 (97)
Total discontinuations, n (%)	9 (3)	7 (2.3)	16 (3)
Withdrawal by subject	5 (2)	1 (0.3)	6 (1)
Protocol violation <sup>a</sup>	2 (0.7)	1 (0.3)	3 (0.5)
Adverse event	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow-up	0	2 (0.7)	2 (0.3)
Other <sup>b</sup>	1 (0.3)	2 (0.7)	3 (0.5)

a. protocol violation PiPr subject: scope incomplete d/t poor quality of prep; PiPr subject could not return for Visits 4 and 5; HL subject: prep did not work

b. Other: PiPr subject: Visit 3 colonoscopy could not be performed d/t power outage at site; HL subject forgot and another HL subject unable to return for visit 6.

Source: Sponsor's Table 7 -1, CSR FE2009-02,p.41/ 81.

### Protocol Deviations

A protocol deviation was defined as any variance from the criteria for the enrollment and conduct of the study, as specified in the protocol. Prior to study unblinding, a blinded review of all subjects with protocol deviations was conducted to determine which subjects had deviations that met the criteria specified in the SAP for exclusion from the PP analysis set.

- Violation of any of the protocol inclusion or exclusion criteria.
- Violation of the dosing regimen, as recorded on the CRF, including the amount and time of study drug administration.
- Receiving incorrectly randomized study drug.

- Taking exclusionary medications during the study and/or prior to the procedure.

**Study FE2009- 01(Split dosing)- Protocol Deviations:**

Of the 601 subjects who received study drug and had a colonoscopy performed- 27 subjects in the PICOPREP treatment group and 23 subjects in the HalfLyte treatment group met the protocol-defined criteria for exclusion from the PP analysis set. Violations of inclusion/exclusion criteria were primarily screening laboratory values outside the normal range for which the sponsor gave a waiver.

Major protocol deviations that led to exclusion from the PP analysis set in the PICOPREP treatment group included:

- Inclusion/exclusion violation (primarily laboratory values outside normal range): Subjects 101-003, 101-010, 101-012, 101-029, 101-046, 101-073, 101-100, 101-125, 103-009, 103-010, 103-036, 103-041, 103-055, 105-014, 105-039, 106-113, 110-014, 110-016.
- Exclusionary medication taken (drugs not permitted in combination with study drug and/or suspended prior to study drug administration) These drugs included lithium, laxatives (suspended 24 hours prior to procedure),
- Constipating drugs (suspended for 2 days prior to procedure), antidiarrheals (suspended for 72 hours prior to procedure), and oral iron preparations (suspended for 1 week prior to procedure) :Subjects 101-081, 101-095, 102-024, 102-058, 107-075, 109-021, 110-001, and 110-016.
- Incomplete efficacy assessments: Subjects 104-038, 105-021.
- Incorrect randomization of treatment kit: Subject 110-021(randomized to kit# 100553 and inadvertently dispensed kit#100533)

The major protocol deviations that led to exclusion from the PP analysis set in the HalfLyte treatment group included :

- Inclusion/exclusion violation: Subjects 101-025, 101-027, 101-123, 101-126, 103-008, 103-024, 103-027, 103-049, 105-022, 105-024, 105-026, 105-045, and 110-009.
- Exclusionary medication taken: Subjects 101-042, 104-016, 107-005, 107-029, 107-082, 109-005, and 110-015.
- Incomplete efficacy assessments: Subjects 104-038, 105-021

- Incorrect randomization of treatment kit: Subject 110-002 (randomized to kit #100533 and inadvertently dispensed kit #100553)

Minor deviations included study visits outside of the visit window, missed visits, and missed study procedure, noncompliance with the preparation, and addition to medical history after randomization.

**Study FE2009- 02(Day Before dosing)- Protocol Deviations:**

Major protocol deviations that led to exclusion from the PP analysis set in the PICOPREP treatment group included:

- Inclusion/exclusion criteria violation: Subjects 202-045, 202-047, 203-051, 203-057, 204-010, 204-014, 204-024, 204-033, 204-045, 204-052, 205-023, 205-030, 206-001, 208-004, 208-053, 208-057, 210-030, 210-055
- Exclusionary medication taken: Subjects 203-020, 203-063, 204-043, 205-025, 205-045, 207-010, 207-028, 207-032, 207-033, 208-034, 212-076, 212-086
- Incomplete efficacy assessments: Subjects 202-042, 204-044, 209-028
- Violation of dosing regimen: Subjects 210-053 and 210-055

Major protocol deviations that led to exclusion from the PP analysis set in the HalfLyte treatment group included:

- Inclusion/exclusion criteria violation: Subjects 202-017, 203-041, 205-027, 205-036, 208-010, 208-011, 208-025, 208-049, 210-014, 210-031, 210-045, 210-049
- Exclusionary medication taken: Subjects 201-004, 203-005, 204-054, 206-004, 208-006, 208-008, 208-016, 211-033

Three subjects were discontinued due to protocol deviations (PicoPrep Subject 202-042: scope incomplete due to poor quality of the prep; PicoPrep Subject 212-048: patient could not return to site for Visits 4 and 5; HalfLyte Subject 211-039: prep did not work).

No subjects were incorrectly randomized in Study 02.

## 6.1.4 Analysis of Primary Endpoint(s)

### Efficacy Evaluation for Study FE2009-01 Split Dose dosing

The non-inferiority of PICOPREP to HalfLyte was demonstrated in the primary efficacy variable, overall colon cleansing based on the Aronchick Scale, and in the key secondary variable, ascending colon cleansing based on the Ottawa Scale. Subsequently, as prespecified in the statistical analysis plan, the lower bound of the CI was determined to be >0%, and the superiority of PICOPREP for overall colon cleansing and ascending colon cleansing was declared.

#### Primary Efficacy Endpoint

The primary efficacy variable was the Aronchick Scale rating of overall colon cleansing in preparation for colonoscopy. Subjects with an excellent or good rating on the scale at Visit 3 during colonoscopy were defined as responders. Non-inferiority was demonstrated if the 1-sided 97.5% CI for the treatment difference (PICOPREP minus HalfLyte) was >-9% for the percentage of responders.

#### Study FE2009-01 (Split-dosing)

The lower bound of the 1-sided 97.5% CI for the treatment difference was 3.4% in the ITT analysis set and 2.7% in the PP analysis set; thus, the NI of PICOPREP to HalfLyte was demonstrated in both analysis sets. Subsequently, as prespecified in the statistical analysis plan, the lower bound of the CI was determined to be >0%, and the superiority of PICOPREP was declared. For both analysis sets, the percentage of responders in the PICOPREP group was greater than in the HalfLyte group.

Table 9 Non-inferiority Analysis for Percentage of Responders Using the Aronchick Scale at Visit 3 (ITT and PP Analysis Sets)

Analysis Set	Statistic	PICOPREP	HalfLyte	Treatment Δ (PP-HL)	1-Sided 97.5% CI
Intent-to-Treat	N	304	297	10	3.4 <sup>b</sup>
	Responders <sup>a</sup> n(%)	256 (84)	221 (74)		
Per Protocol	N	277	274	9	2.7 <sup>b</sup>
	Responders <sup>a</sup> n(%)	235 (85)	207 (76)		

HalfLyte Subjects 104-038 and 105-021 with unknown responder status were classified as treatment failures in the ITT analysis set.

a. Excellent or good rating

b. Non-inferior and superior

Source: Sponsor's Table9-1, CSR FE2009-01, page 49/80.

Table 10 Study FE2009-01 Reviewer’s Analysis-Based on dataset “ADFA” submitted by the Sponsor (ITT)

<b>Aronchick Scale</b>	<b>PicoPrep (n=304)</b>	<b>HalfLyteLy (n=295)</b>	<b>Total (N=599)</b>
Excellent	139 <b>(46%)</b>	100 <b>(34%)</b>	239
Good	117 (38.5%)	121 (41%)	238
Fair	47 (15%)	70 (24%)	117
Inadequate	1 <b>(0.3%)</b>	4 <b>(1%)</b>	5

P-Value for Chi-Square 0.006

Table reproduced from Biometrics Review, Dr. Shahla Farr page 19.

Table 11 Study FE2009-01 Reviewer’s Analysis-Based on dataset “ADFA” submitted by the Sponsor (PP)

<b>Aronchick Scale</b>	<b>PicoPrep (n=277)</b>	<b>HalfLyteLy (n=274)</b>	<b>Total (N=551)</b>
Excellent	127 <b>(46%)</b>	98 <b>(36%)</b>	225
Good	108 (39%)	109 (40%)	217
Fair	42 (15%)	64 (23%)	106
Inadequate	0 <b>(0%)</b>	3 <b>(1%)</b>	3

P-Value for Chi-Square 0.01

Table reproduced from Biometrics Review, Dr. Shahla Farr page 19.

### **Study FE2009-02 (Day Before dosing)**

The lower bound of the 1-sided 97.5% CI for the treatment difference was --2.9% in the ITT analysis set and -2.8% in the PP analysis set; thus, the NI of PICOPREP to HalfLyteLy was demonstrated in both analysis sets. Subsequently, as prespecified in the statistical analysis plan, the lower bound of the CI was determined to be >0%, and the superiority of PICOPREP was declared. For both analysis sets, the percentage of responders in the PICOPREP group was greater than in the HalfLyteLy group.

Table 12 Non-inferiority Analysis for Percentage of Responders Using the Aronchick Scale at Visit 3 (ITT and PP Analysis Sets)

Analysis Set	Statistic	PICOPREP	HalfLyteLy	Treatment Δ (PP-HL)	1-Sided 97.5% CI
Intent-to-Treat	<b>N</b> Responders <sup>a</sup> n(%)	<b>294</b> 244 (83)	<b>300</b> 239(80)	<b>3</b>	<b>-2.9<sup>b</sup></b>
Per Protocol	<b>N</b> Responders <sup>a</sup> n(%)	<b>260</b> 216 ( <b>83</b> )	<b>280</b> 222 ( <b>79</b> )	<b>4</b>	<b>-2.8<sup>b</sup></b>

HalfLyteLy Subjects 104-038 and 105-021 with unknown responder status were classified as treatment failures in the ITT analysis set.

a. Excellent or good rating

b. Non-inferior

Source: Sponsor's Table 9-1, CSR FE2009-02, p.49/81

Table 13 Study FE2009-02 Reviewer's Analysis –Based on dataset"ADFA" submitted by the Sponsor (ITT)

Aronchick Scale	PicoPrep (n=294)	HalfLyteLy (n=300)	Total (N=594)
Excellent	143 ( <b>49%</b> )	121 ( <b>40%</b> )	264
Good	101 (34%)	118 (39%)	219
Fair	46 (16%)	56 (19%)	102
Inadequate	4 ( <b>1%</b> )	5 ( <b>2%</b> )	9

P-Value for Chi-Square 0.2

Table reproduced from Biometrics Review, Dr. Shahla Farr page 23

Table 14 Study FE2009-02 Reviewer's Analysis –Based on dataset"ADFA" submitted by the Sponsor (PP)

Aronchick Scale	PicoPrep (n=260)	HalfLyteLy (n=280)	Total (N=540)
Excellent	126 (48%)	113 (40%)	239
Good	90 (35%)	109 (39%)	199
Fair	42 (16%)	53 (19%)	95
Inadequate	2 (1%)	5 (2%)	7

P-Value for Chi-Square 0.2

Table reproduced from Biometrics Review, Dr. Shahla Farr page 23

### 6.1.5 Analysis of Secondary Endpoints(s)

#### Ascending Colon Cleansing

The protocol-defined, key secondary efficacy variable was the percentage of subjects classified as a clinical success (responder) for cleansing the ascending colon at Visit 3 during the colonoscopy, where success was defined as a rating of Excellent, Good, or Fair (0, 1, or 2, respectively) on the Ottawa Scale. Non-inferiority was demonstrated if the 1-sided 97.5% CI for the treatment difference (PICOPREP minus HalfLyte) was >-9% for the percentage of responders.

#### **Study FE2009-01 (Split-dosing)**

Based on the Sponsor's results the percentage of responders for PICOPREP was greater than for HalfLyte for cleansing the ascending colon in both the ITT analysis set (90% versus 79%) and the PP analysis set (90% versus 79%). The non-inferiority of PICOPREP to HalfLyte in cleansing the ascending colon was demonstrated in both analysis sets. Subsequently the bound of the CI was determined to be >0% and the superiority of PICOPREP was declared in both the ITT and PP analysis sets.

Table 15 Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale at Visit 3 (Day of procedure), ITT and PP Analysis Sets

Population	PICOPREP n/N(%)	HalfLyte n/N(%)	Treatment Δ (PP-HL)	1-Sided 97.5% CI
<b>Intent-To-Treat Responders<sup>a</sup></b>	<b>272/304 (90)</b>	<b>234/297 (79)</b>	<b>11</b>	<b>4.9<sup>b</sup></b>
<b>Per Protocol Responders<sup>a</sup></b>	<b>250/277 (90)</b>	<b>217/274 (79)</b>	<b>11</b>	<b>5.1<sup>b</sup></b>

PICOPREP Subject 103-019 and HalfLyte Subjects 104-038 and 105-021 with unknown responder status were classified as treatment failures in the ITT analysis set.

a. Excellent or good rating

b. Non-inferior and superior

Source: Sponsor's Table 9-3, CSR FE-2009-01, p.50/80.

Table 16 Reviewers Analysis - Based on dataset "ADFA" submitted by the Sponsor (ITT) Secondary Endpoint (OTTAWA Score = Ascending)

Ottawa Scale (Ascending)	PicoPrep (n=303)	HalfLyte (n=295)	Total (N=598)
Excellent	51 (17%)	21 (7%)	72
Good	76 (25%)	58 (20%)	134
Fair	145 (48%)	155 (53%)	300
Poor	29 (10%)	56 (19%)	85
Inadequate	2 (1%)	5 (2%)	7

P-Value for Chi-Square 0.0001

Reproduced from Biometrics review, Dr. Shahla Farr, page 22.

**Study FE2009-02 (Day before dosing)**

The percentage of responders for PICOPREP and HalfLyte for cleansing the ascending colon in the ITT analysis set was (81% versus 84%). The NI of PICOPREP to HalfLyte in ascending colon cleansing was demonstrated in the ITT analysis set. In the PP analysis set, the percentage of responders was 81% for PICOPREP and 85% for HalfLyte.

Table 17 Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale at Visit 3 (Day of procedure), ITT and PP Analysis Sets

Population	PICOPREP n/N (%)	HalfLyte n/N (%)	Treatment Δ (PP-HL)	1-Sided 97.5% CI
Intent-To-Treat Responders <sup>a</sup>	239/294 (81)	252/300 (84)	-3	-8.8 <sup>b</sup>
Per Protocol Responders <sup>a</sup>	211/260 (81)	237/280 (85)	-4	-9.8 <sup>b</sup>

PICOPREP Subject 202-042 and 202-044 with unknown responder status were classified as treatment failures.

a. Excellent, good, or fair rating

b. Non-inferior and superior

Source: Sponsor's Table 9-3, CSR FE-2009, p.51/81.

Table 18 Reviewers Analysis - Based on dataset “ADFA” submitted by the Sponsor (ITT) Secondary Endpoint (OTTAWA Score = Ascending)

<b>Ottawa Scale (Ascending)</b>	<b>PicoPrep (n=292)</b>	<b>HalfLyte (n=300)</b>	<b>Total (N=592)</b>
<b>Excellent</b>	<b>43 (15%)</b>	<b>31 (10%)</b>	<b>74</b>
<b>Good</b>	<b>89 (30%)</b>	<b>99 (33%)</b>	<b>188</b>
<b>Fair</b>	<b>107 (37%)</b>	<b>122 (41%)</b>	<b>229</b>
<b>Poor</b>	<b>50 (17%)</b>	<b>48 (16%)</b>	<b>98</b>
<b>Inadequate</b>	<b>3 (1%)</b>	<b>0</b>	<b>3</b>

P-Value for Chi-Square 0.17

Reproduced from Biometrics review, Dr. Shahla Farr, page 26.

### **Subject Acceptability and Tolerability Questionnaire Study FE2009-01 (Split-dosing)**

The distribution of subject ratings of tolerability and satisfaction for PICOPREP was statistically significantly superior ( $p < 0.0001$ ) to subject ratings for HalfLyte on all questions.

Some of the clinically important treatment group differences were:

- 1) The preparation was rated as easy or very easy to consume by 89.4% of PICOPREP subjects as compared to 29.1% of HalfLyte subjects.
- 2) The overall experience was rated as excellent by 46.8% of PICOPREP subjects as compared to 16.6% of HalfLyte subjects.
- 3) The taste of the preparation was rated as excellent or good by 73.9% of PICOPREP subjects as compared to 21.5% of HalfLyte subjects.
- 4) A larger percentage of subjects in the PICOPREP than in the HalfLyte group would ask their doctor for the preparation again for a future colonoscopy (96.0% versus 54.7%).

### **6.1.6 Other Endpoints**

#### **Cleansing of Other Colon Segments**

##### **Study FE2009-01 (Split-dosing)**

Further analysis of efficacy was conducted for cleansing the mid colon and recto-sigmoid colon, as well as a fluid assessment (small, moderate, or large amount). For the ITT and PP analysis sets, the percentage of responders for PICOPREP was greater than for HalfLyte for cleansing the mid colon (92.4% versus 85.9% and 92.8% versus 86.5%, respectively) and the recto-sigmoid colon (92.4% versus 87.2% and 92.4% versus 87.6%, respectively).

The non-inferiority of PICOPREP to HalfLyte was demonstrated in both the ITT and PP analysis sets for both colon segments.

Subsequently, the bound of the CI was determined to be >0% for both colon segments in the ITT analysis set and the superiority of PICOPREP was declared. In the PP analysis set, the superiority of PICOPREP was declared for cleansing the mid colon segment.

In addition, the responder rate across colon segments for the Ottawa Scale demonstrated the non-inferiority of PICOPREP to HalfLyte in the ITT analysis set. The percentage of responders for PICOPREP was greater than for HalfLyte for overall colon cleansing of the ascending, mid, and recto-sigmoid colon (87% versus 75%). Given that the bound of the CI was >0%, the superiority of PICOPREP was declared for overall colon cleansing.

Table 19 Non-inferiority Analysis for Percentage of Responders by Colon Segment Using the Ottawa Scale, Visit 3 (ITT and PP Analysis Sets)

Population	Area of colon	PICOPREP n/N (%)	HalfLyteLy n/N (%)	Treatment Δ (PP-HL)	1-Sided 97.5% CI
<b>Intent-To-Treat Responders<sup>a</sup></b>	Ascending colon	272/304 <b>(90)</b>	234/297 <b>(79)</b>	<b>11</b>	<b>4.9<sup>b</sup></b>
	Mid colon	281/304 (92)	255/297 <b>(86)</b>	<b>7</b>	<b>1.6<sup>b</sup></b>
	Recto-sigmoid colon	281/304 <b>(92)</b>	259/297 <b>(87)</b>	<b>5</b>	<b>0.4<sup>b</sup></b>
	Overall:Asc, mid, and recto-sig colon	264/304 <b>(87)</b>	224/297 <b>(75)</b>	<b>11.4</b>	<b>5.2<sup>b</sup></b>
<b>Per Protocol Responders<sup>a</sup></b>	Ascending colon	250/277 <b>(90)</b>	217/274 <b>(79)</b>	<b>11</b>	<b>5.1<sup>b</sup></b>
	Mid colon	257/277 <b>(93)</b>	237/274 <b>(87)</b>	<b>6</b>	<b>1.2<sup>b</sup></b>
	Recto-sigmoid colon	256/277 <b>(92)</b>	240/274 <b>(88)</b>	<b>4</b>	<b>-0.2<sup>c</sup></b>

PICOPREP Subject 103-019 with unknown responder status for the ascending colon and HalfLyteLy Subjects 104-038 and 105-021 with unknown responder status for the ascending and mid colon were classified as treatment failures ITT

- a. Excellent or good rating
- b. Non-inferior and superior
- c. Non-inferior

Source: Sponsor's Table 9-4, CSR FE2009-01, p.51/80.

## Fluid Assessment

### Study FE2009-01 (Split-dosing)

The percentage of subjects in each category of fluid quantity are summarized in the following table. The number of subjects in each fluid quantity category (small, moderate, or large) were generally similar between the 2 treatment groups. No statistically significant difference existed between the ITT and PP analysis sets.

Table 20 Fluid Assessment at Visit 3 (ITT and PP Analysis Sets)

Analysis Set	Fluid Assessment Category	Number (%) of Subjects	
		PICOPREP N=303	HalfLyteLy N=296
Intent-To-Treat <sup>a</sup>	Small	185 (61)	165 (58)
	Moderate	98 (32)	113 (38)
	Large	20 (7)	18 (6)
Per Protocol	Small	165 (60)	156 (57)
	Moderate	92 (33)	103 (38)
	Large	20 (7)	15 (6)

a. PICOPREP Subject 101-095 and HalfLyteLy Subject 104-038 were missing a fluid assessment and were excluded from the analysis. Source: Summary Table 14.2.2.5  
Source: Sponsor's Table 9-5, CSR FE2009-01, p.52/80.

### Colon Cleansing of other colon segments Study FE2009-02 Day-Before dosing

As in Study FE2009-01, further analysis of efficacy was conducted for cleansing the mid colon and recto-sigmoid colon, as well as a fluid assessment (small, moderate, or large amount). For the ITT analysis set and PP analysis sets, the percentage of responders for PICOPREP was greater than for HalfLyteLy for cleansing the mid colon (93.2% versus 88.7%, and 95.0% versus 88.9%, respectively) and the recto-sigmoid colon (92.2% versus 89.0%, and 93.5% versus 89.6%, respectively). In both analysis sets, the NI of PICOPREP to HalfLyteLy was demonstrated for both the mid colon and

rectosigmoid colon segments. Subsequently, the bound of the CI was determined to be >0% for the mid colon segment in the PP analysis set and the superiority of PICOPREP was declared.

Additionally, the responder rate across colon segments for the Ottawa Scale demonstrated the NI of PICOPREP to HalfLyte in the ITT analysis set. The percentage of responders for PICOPREP and HalfLyte was similar for overall colon cleansing of the ascending, mid, and recto-sigmoid colon (79% versus 78.0%).

The results of the Ottawa Scale are presented by colon segment for ITT and PP analysis sets in the table below.

Table 21 Non-inferiority Analysis for Percentage of Responders by Colon Segment Using the Ottawa Scale, Visit 3 (ITT and PP Analysis Sets)

Population	Area of colon	PICOPREP n/N (%)	HalfLytely n/N (%)	Treatment Δ (PP-HL)	1-Sided 97.5% CI
<b>Intent-To-Treat Responders<sup>a</sup></b>	Ascending colon	239/294 <b>(81)</b>	252/300 <b>(84)</b>	<b>-3</b>	<b>-8.8<sup>b</sup></b>
	Mid colon	274/294 <b>(93)</b>	266/300 <b>(89)</b>	<b>4.5</b>	<b>-0.1<sup>b</sup></b>
	Recto-sigmoid colon	271/294 <b>(92)</b>	267/300 <b>(89)</b>	<b>3.2</b>	<b>-1.5<sup>b</sup></b>
	Overall:Asc, mid, and recto-sig colon	232/294 <b>(79)</b>	234/300 <b>(78)</b>	<b>0.9</b>	<b>-5.7<sup>b</sup></b>
<b>Per Protocol Responders<sup>a</sup></b>	Ascending colon	211/260 <b>(81)</b>	237/280 <b>(79)</b>	<b>-4</b>	<b>-9.8</b>
	Mid colon	247/260 <b>(95)</b>	249/280 <b>(87)</b>	<b>6</b>	<b>1.5<sup>c</sup></b>
	Recto-sigmoid colon	243/260 <b>(94)</b>	251/280 <b>(88)</b>	<b>4</b>	<b>-0.8<sup>b</sup></b>

PICOPREP Subject 103-019 with unknown responder status for the ascending colon and HalfLytely Subjects 104-038 and 105-021 with unknown responder status for the ascending and mid colon were classified as treatment failures ITT

a. Excellent, good, or fair rating

b. Non-inferior

c. Non-inferior and superior

Source: Sponsor's Table 9-4, CSR FE2009-02, p.52/81.

### **Fluid Assessment** **Study FE2009-02 Day-Before dosing**

The percentage of subjects in each category of fluid quantity are summarized in the table below. The number of subjects in each fluid quantity category (small, moderate, or large) were generally similar between the 2 treatment groups. No statistically significant difference existed between the ITT (p=0.0710) and PP (p= 0.1507) analysis sets.

Table 22 Fluid Assessment at Visit 3 (ITT and PP Analysis Sets)

Analysis Set	Fluid Assessment Category	Number (%) of Subjects	
		PICOPREP N=292	HalfLyteLy N=300
Intent-To-Treat <sup>a</sup>	Small	180 (62)	163 (54)
	Moderate	99 (34)	120 (40)
	Large	13 (5)	17 (6)
Per Protocol	Small	157 (60)	153 (55)
	Moderate	92 (35)	110 (39)
	Large	11 (4)	17 (6)

Source: Sponsor's Table 9-5, CSRFE2009-02, p. 53/81.

**Subject Acceptability and Tolerability Questionnaire  
 Study FE2009-02 Day-Before dosing**

The distribution of subject ratings of tolerability and satisfaction for PICOPREP was statistically significantly superior ( $p < 0.0001$ ) to subject ratings for HalfLyteLy on all questions.

Some of the clinically important treatment group differences were:

- 1) The preparation was rated as easy or very easy to consume by 87.4% of PICOPREP subjects and 37.2% of HalfLyteLy subjects.
- 2) The overall experience was rated as excellent by 45.5% of PICOPREP subjects and 19.1% of HalfLyteLy subjects.
- 3) The taste of the preparation was rated as good or excellent by 73.7% of PICOPREP subjects and 27.9% of HalfLyteLy subjects.
- 4) A larger percentage of subjects in the PICOPREP than in the HalfLyteLy group would ask their doctor for the preparation again for a future colonoscopy (93.2% versus 59.4%).

**Reviewer's Comment: The Acceptability and Tolerability Questionnaire provides subjective commentary that may inform the sponsor's marketing strategy. The efficacy analyses are not impacted by this additional information.**

### 6.1.7 Subpopulations

Additional analyses were performed by the Biometrics reviewer to determine the response rates using the Aronchick Scale by age, gender, and race. Patients ranged in age from 18 to 80 years mean age 56 years. 61% of patients were female while 39% of patients were male. Self-identified race was distributed as follows: 90% White, 10% Black, and 0.7% other. Of these, 3% self-identified their ethnicity as Hispanic or Latino. In the controlled trials of PICOPREP, 215 of 1201 (18%) of patients were 65 years of age or older, and 25 (2.1%) were 75 years of age or older.

Table 23 Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Age Category - Both Studies Combined (ITT)

Age Category	PicoPrep (n=598)	HalfLyteLy (n=595)	P-Value Difference 95% CI
16 – 64	409/486 (84%)	388/493 (79%)	0.03 5% (1%, 10%)
>= 65	91/112 (81%)	72/102 (71%)	0.7 11% (-1%, 22%)

Table 24 Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Gender - Both Studies Combined (ITT)

Gender	PicoPrep (n=598)	HalfLyteLy (n=595)	P-Value Difference 95% CI
Female	317/371 (85%)	293/359 (82%)	0.2 4% (-2%, 9%)
Male	183/227 (81%)	167/236 (71%)	0.1 10% (2%, 17%)

Table 25 Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Race - Both Studies Combined (ITT)

<b>Race</b>	<b>PicoPrep (n=598)</b>	<b>HalfLytely (n=595)</b>	<b>P-Value Difference 95% CI</b>
<b>White</b>	<b>446/536 (83%)</b>	<b>411/532 (77%)</b>	<b>0.01 6% (1%, 11%)</b>
<b>Blake or African American</b>	<b>50/58 (86%)</b>	<b>45/58 (76%)</b>	<b>0.2 9% (-5%, 23%)</b>

The other racial groups had very small populations (between 1 to 5 subjects) therefore, no conclusions could be drawn.

**Reviewer’s Comment: The subpopulation analyses were conducted by the Biometrics reviewer by request from this reviewer. The tables are sourced from the request for analyses and are not in the Biometrics review.**

### **6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

No additional clinical information was reviewed relevant to dosing recommendations.

### **6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

PICOPREP is indicated for a one time use as a bowel preparation before colonoscopy. No issues were seen with persistence of efficacy or tolerance effects.

### **6.1.10 Additional Efficacy Issues/Analyses**

There are no additional efficacy issues or analyses that have not been described in other parts of this review.

## **7 Review of Safety**

### **Safety Summary**

The clinical program supporting the safety of PICOPREP for cleansing of the colon as a preparation for colonoscopy in adults in the United States primarily consists of integrated data from 2 Phase 3, randomized, multicenter clinical trials Studies FE2009-01 (Split-dosing) and FE2009-02 (Day-before dosing).

## 7.1 Methods

In the Phase 3 studies, safety was evaluated by collection of adverse events, physical examinations, vital signs, clinical laboratory tests, and electrocardiograms (ECGs). Investigators monitored subjects for clinical and laboratory evidence of adverse events throughout the studies. Abdominal bloating, distension, pain/cramping, and watery diarrhea were clinical changes that, if noted by the subject, were not to have been documented as adverse events, unless the findings induced an action (e.g., led the study discontinuation).

Physical examinations were conducted and vital signs (orthostatic blood pressure and pulse rate) were collected at each visit. Samples for laboratory determinations (hematology, coagulation, chemistry, urinalysis) were collected and 12-lead ECGs were performed at Visits 1 (Baseline), 3 (day of colonoscopy), 4 (24-48 hours after the procedure),

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

To demonstrate safety and efficacy of PICOPREP, 2 large Phase 3 studies, FE2009-01 and FE2009-02, were conducted entirely in the United States, which compared PICOPREP to the commercially available HalfLytely® and Bisacodyl Tablets Bowel Prep Kit (hereafter referred to as HalfLytely) for colon cleansing in preparation for a colonoscopy procedure. Both studies were randomized, assessor-blinded, non-inferiority, multi-center trials. Twenty investigator sites in the United States randomly assigned 1211 adult subjects requiring colonoscopy to receive PICOPREP (607 subjects) or HalfLytely (604 subjects) in a one-to-one ratio; 1201 subjects received at least 1 dose of study drug (601 PICOPREP and 600 HalfLytely).

Each dose of PICOPREP consisted of 2 pouches of powder for oral solution (mixed in 5 ounces of water), administered separately following 1 of 2 dosing regimens (“Split-Dose” or “Day-Before”).

In Study FE2009-01, PICOPREP (Split-Dose dosing regimen) was administered between 5:00 PM and 9:00 PM in the evening before the colonoscopy (first reconstituted pouch) and then again in the morning of the colonoscopy (second reconstituted pouch) at least 5 hours prior to but no more than 9 hours prior to the procedure.

In Study FE2009-02, PICOPREP (Day-Before dosing regimen) was administered between 4:00 PM and 6:00 PM (first reconstituted pouch) and again approximately 6 hours later (second reconstituted pouch), both on the day prior to colonoscopy. With either regimen, five (5) 8-ounce glasses of clear liquids were to be consumed after the

first pouch administration and three (3) 8-ounce glasses of clear liquids were to be consumed after the second pouch administration.

In both studies, HalfLytely was administered per product labeling approved at the time the studies were designed, consisting of two (2) 5-mg bisacodyl tablets in the afternoon on the day prior to colonoscopy, followed by timed drinking of the HalfLytely solution at a rate of one (1) 8-ounce glass every 10 minutes after the first bowel movement or after 6 hours, whichever occurred first. In both studies, the HalfLytely group completed treatment the day prior to colonoscopy as per labeled instructions.

The studies consisted of 6 visits, including Screening (Visit 1), day of randomization (Visit 2), day of colonoscopy (Visit 3), and 24-48 hours (+1 day), 7 days (+3 days), and 4 weeks (□5 days) after the procedure (Visits 4, 5, and 6, respectively). Safety was evaluated by collection of adverse events, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations.

### 7.1.2 Categorization of Adverse Events

Investigators monitored subjects for clinical and laboratory evidence of adverse events throughout the studies. Adverse events were defined as any untoward medical occurrence in a clinical investigation subject administered an investigational medicinal product (IMP), which did not necessarily have a causal relationship with the treatment.

An adverse event could have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IMP, whether or not the event was considered related to the IMP.

Abdominal bloating, distension, pain/cramping, and watery diarrhea were clinical changes that, if noted by the subject, were not to have been documented as adverse events, unless the findings induced an action, such as:

- Led to changes in study medication or to study discontinuation;
- Led to therapeutic or diagnostic procedures;
- Met the criteria for a serious adverse event; or
- Showed clinically significant worsening during the study, which was not in the frame of the usual clinical course, as determined by the investigator.

The intensity of adverse events was rated by the investigators according to the following definitions:

Mild	Awareness of signs or symptoms but no disruption of usual activity
Moderate	Event sufficient to affect usual activity (disturbing)
Severe	Inability to work or perform usual activities (unacceptable)

Investigators also assessed the causal relationship of each adverse event to the use of the IMP according to the following definitions:

Probable	Clear temporal association with improvement on cessation of the IMP or reduction in dose. Reappeared upon re-challenge. Followed a known pattern of response to the IMP.
Possible	Followed a reasonable temporal sequence from administration. May have been produced by the subject's clinical state, environmental factors, or other therapies administered.
Unlikely	Did not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state, environmental factors, or other therapies administered.
Unrelated	Clearly and incontrovertibly due only to extraneous causes and did not meet criteria listed under unlikely, possible, or probable.

Serious adverse events were defined as any untoward medical occurrence that at any dose resulted in death; was life-threatening; required in-patient hospitalization or prolonged existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; or was an important medical event.

An adverse event caused by overdose or medical error was considered serious if a previously listed criterion was fulfilled, as well as any suspected transmission of an infectious agent through a medicinal product.

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

The integrated Safety Analysis Set was used to summarize the integrated safety data across Studies FE2009-01 and FE2009-02 using the safety datasets from the individual studies. The Safety Analysis Set, as defined for the individual studies, was the collected data from all subjects who received at least 1 dose of study medication. Treatment assignment for summary and analysis was based on actual treatment taken.

In Studies FE2009-01 and FE2009-02 combined, the most commonly reported ( $\geq 10.0\%$  of subjects) treatment-emergent adverse events in both treatment groups were resultant findings of the colonoscopy procedure, including hemorrhoids, diverticulae, colon adenoma, and colon polyps.

No treatment-group differences were noted for the incidences of any specific treatment-emergent adverse event.

The majority of the treatment-emergent adverse events reported were considered by the investigator to be mild or moderate in intensity. Treatment-emergent adverse events indicated as severe in intensity were reported for 7 (1.2%) subjects in the PICOPREP treatment group and 12 (2.0%) subjects in the HalfLytely treatment group

In the PICOPREP treatment group, treatment-emergent adverse events designated by the investigator as severe in intensity included single events of diverticulum, scar (colon scar tissue), colon cancer, anastomotic complication, dehydration, acute coronary syndrome, esophagitis, headache, pancreatitis acute, and abdominal pain. Except for the event of headache. Each of these events was considered unrelated or unlikely to be related to study drug by the Investigator.

The severe headache event was experienced by Subject 212-072, a 49-year-old white female. The event started on Study Day 1 after experiencing forceful vomiting following ingestion of PICOPREP. By Study Day 10, the headache persisted and the subject was evaluated by computed tomography (CT) scan, which showed abnormalities. An event of cerebral hemorrhage was reported, which was considered unlikely to be related to study drug. None of these events was designated as serious.

In the HalfLytely treatment group, treatment-emergent adverse events designated by the investigator as severe in intensity included 2 events of abdominal pain, and single events of ileus, procedural pain, arthropod bite, sinusitis, dizziness, diverticulum intestinal, colon cancer, diarrhea, nausea, vomiting, back pain, arthralgia, and rheumatoid arthritis. Each of these events was considered unrelated or unlikely to be related to study drug, except for the event of dizziness and 1 event of abdominal pain.

The severe dizziness event was experienced on Study Day 1 by Subject 212-018, a 57-year-old white female; no treatment was specified for the event and it was noted as resolved on Study Day 1.

The severe abdominal pain event was experienced on Study Day 3 by Subject 107-004, a 49-year-old white female; no treatment was specified for the event and it was noted as resolved on Study Day 6.

A summary of treatment emergent adverse events experienced by > 2% of subjects in either treatment group for Studies FE20009-01 (split dose) and FE2009-02 (day before dose) combined is presented in the table below

Table 26 Treatment –Emergent Adverse Events Experienced by >2.0% of Subjects in Either Treatment Group (Safety Analysis Set)

Category System -Organ-Class Preferred Term	PICOPREP N=601 n (%)	HalfLyteLy N=600 n (%)
Any treatment-emergent adverse event	429 (71.4)	458 (76.3)
Gastrointestinal disorders	345 (57.4)	388 (64.7)
Haemorrhoids	139 (23.1)	140 (23.3)
Diverticulum	123 (20.5)	157 (26.2)
Colonic polyp	89 (14.8)	98 (16.3)
Diverticulum intestinal	38 (6.3)	39 (6.5)
Nausea	26 (4.3)	30 (5.0)
Rectal polyp	25 (4.2)	27 (4.5)
Vomiting	11 (1.8)	19 (3.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	115 (19.1)	118 (19.7)
Colon adenoma	103 (17.1)	108 (18.0)
Nervous system disorders	32 (5.3)	23 (3.8)
Headache	23 (3.8)	17 (2.8)

Subjects with multiple events in the same treatment-emergent adverse event category are counted only once for the treatment-emergent adverse event category. Source: ISSTable 3.2.1

### Drug Related Treatment -Emergent Adverse Events

In Studies FE2009-01 and FE2009-02 combined the overall incidence of drug related adverse events was 8.7% in the PICOPREP treatment group and 9.2% in the HalfLyteLy treatment group. Nausea, vomiting, and headache were the only TEAEs reported by >1% of subjects in both treatment groups.

Table 27 Drug-Related Treatment –Emergent Adverse Events Experienced by >1% of Subjects in Either Treatment Group (Safety Analysis Set)

Category System -Organ-Class Preferred Term	PICOPREP N=601 n (%)	HalfLyteLy N=600 n (%)
Any drug-related• treatment-emergent adverse event	52(8.7)	55 (9.2)
Gastrointestinal disorders	28 (4.7)	38 (6.3)
Nausea	17 (2.8)	24 (4.0)
Vomiting	7 (1.2)	16 (2.7)
Nervous system disorders	13 (2.2)	12 (2.0)
Headache	13 (2.2)	10 (1.7)

Subjects with multiple events in the same treatment-emergent adverse event category are counted only once for the treatment – emergent adverse event category.

a. Possible or probable relationship, as assessed by the investigator, or records where relationship was missing.

Source: Table 4-3 section 4.1.3 ISS page 30.

**Reviewer’s Comment: The treatment –emergent adverse events and drug related treatment emergent adverse events listed do not constitute new or unexpected signals. They are commonly associated with the use of this drug class. Abdominal bloating, distension, pain/cramping, and watery diarrhea are known to occur in response to colon cleansing preparations and these reactions were documented as adverse events in the clinical trials only if medical intervention was required. Adequate hydration and strict adherence to preparation and dosage instructions may decrease the occurrence of adverse events.**

## 7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), and vital signs, electrocardiograms (ECG) and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population.

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

The dose and duration of PICOPREP was adequate to assess safety and to support the proposed indication of “cleansing of the colon as a preparation for colonoscopy in adults” Patients in both Phase 3 Studies FE2009-01 and FE2009-02 were followed a total of 4 weeks.

The exposure days were not calculated for Studies FE2009-01 (split dose) or FE2009-02 (day before dose). The study medications were dosed either across 2 days PICOPREP (split dose) or dosed on 1 day PICOPREP (day before) or HalfLytely (day before) based on treatment groups. Subject diaries for Study FE2009-01 (split dosing) reveal a higher percentage of PICOPREP subjects than HalfLytely subjects drank all of the study medication (99.7%) and 99.3% of these subjects drank the additional number of glasses of liquid recommended following each dose. For the HalfLytely subjects, 91.4% reportedly drank all of the study medication.

Subject diaries for Study FE2009-02 (day before dosing) reveal, at least 99.7% of the PICOPREP subjects drank all of the study medication, and at least 100% of these subjects drank the required number of glasses of liquid following each dose. For the HalfLytely subjects, 95.2% reported they drank all of the study medication.

The demographic make-up of the pooled safety population was adequate. Most patients were white race and male. For further information regarding Studies FE2009-01 and FE2009-02 demographics, see Section 6.1.2.

### **7.2.2 Explorations for Dose Response**

In the current application, all patients receiving PICOPREP received the same dose 2 sachets. The sachets were either taken as a split dose i.e. one sachet the evening before the procedure and the second sachet taken the morning of the procedure or as a day before dose where both sachets are taken the day before the colonoscopy. There was no exploration for dose response.

### **7.2.3 Special Animal and/or In Vitro Testing**

Please see the Non-clinical review by Dr. Tamal Chakraborti.

### **7.2.4 Routine Clinical Testing**

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the two submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Please see the Clinical pharmacology review by Dr. Dilara Jappari.

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

The studies were adequately designed to allow for safety analyses. The submitted studies also adequately monitored for renal, and cardiology events. The studies did not reveal any new safety signals. The two Phase 3 studies FE2009-01 and FE2009-02 showed PICOPREP used as a split dose or day before dose for colon cleansing in preparation for colonoscopy to be relatively safe and well tolerated.

**Reviewer's Comment: There have been rare reports of serious arrhythmias associated with the use of osmotic laxative products for bowel preparation. While patients were monitored with pre and post procedure electrocardiograms, no formal thorough QT study was conducted prior to submission. However, the risk of arrhythmias is expected to be secondary to electrolyte disturbances such as hypokalemia. Patients with cardiology events occurring within last 3 months, and renal insufficiency were excluded from the study. Class labeling will include warnings for use of the product in patients who may be adversely affected by transient changes in fluid and electrolytes or in patients at increased risk for cardiac arrhythmias or those with impaired renal function.**

### 7.3 Major Safety Results

#### **Study FE2009-01 (Split dose)**

During Study FE2009-01, approximately 69% of patients taking PICOPREP experienced at least one treatment-emergent AE, compared with 73% of patients taking HalfLyte. Compared with those who experienced a TEAE, a smaller percentage of patients in both treatment groups experienced an adverse drug reaction (PICOPREP 6% and HalfLyte 9%). In both treatment groups, most events were mild or moderate in severity. TEAEs indicated as severe were reported for 2 subjects in the PICOPREP treatment group and 6 subjects in the HalfLyte treatment group.

In the PICOPREP treatment group, TEAEs designated as severe included single events of acute pancreatitis and abdominal pain. Each event was considered unrelated or unlikely to be related to the study drug.

In the HalfLyte treatment group TEAEs reported as severe included abdominal pain, colon cancer, back pain, diarrhea, nausea and vomiting and arthralgia related to rheumatoid arthritis. Each event was considered unrelated or unlikely to be related to study drug, except for 1 event of abdominal pain. The severe abdominal pain event was experienced on Study Day 3 by Subject 107-004, a 49-year-old white female; no treatment was specified for the event and it was noted as resolved on Study Day 6.

**Reviewer’s Comment: The most commonly reported treatment emergent adverse events were findings from the colonoscopy and included diverticulae, hemorrhoids, colon adenoma and colon polyps. There were no clinically significant differences noted between the treatment groups for any specific TEAE.. Information about Subject 107-004 was not included in Data Listing 16.2.8 as referenced in the CSR.**

Table 28 Summary of Safety Results (Split-dose Dose)

	Study FE2009-01 (Split dose)	
	PICOPREP N=305	HalfLyte N=298
	n (%)	n (%)
Any treatment emergent AE	211 (69)	217 (73)
Any Severe TEAEs	2 (0.7)	6 (2.0)
Serious Adverse Event (SAE)	1 (0.3)	2 (0.7)
Discontinuation due to TEAEs	0	1 (0.3)
Deaths	0	0
Adverse Drug reactions (ADR)	19 (6)	26 (9)

ADRs are assessed by the Investigator as probably or possibly causally related to study drug.  
 Subjects who had multiple events in the same AE category are counted only once for the AE category  
 Source: Adapted from Table 10-1 (p 59/80) Section 10.1 CSR.

**Study FE2009-02 (Day before dose)**

During Study FE2009-02, approximately 74% of patients taking PICOPREP experienced at least one treatment-emergent AE, compared with 80% of patients taking HalfLyte. Compared with those who experienced a TEAE, a smaller percentage of patients in both treatment groups experienced an adverse drug reaction (PICOPREP 11% and HalfLyte 10%). In both treatment groups, most events were mild or moderate in severity. TEAEs indicated as severe were reported for 5 subjects in the PICOPREP treatment group and 6 subjects in the HalfLyte treatment group.

In the PICOPREP treatment group, TEAEs designated as severe included diverticulum and scar (colon scar tissue)); colon cancer, anastomotic complication and dehydration, acute coronary syndrome, esophagitis, and headache. Each of these events was considered unrelated or unlikely to be related to study drug, except for the event of headache. Subject narratives are provided below.

**Subject 212-072**, On Study Day 1, a 49-year-old white female, developed ADRs of mild vomiting following ingestion of PICOPREP and a severe headache. The vomiting resolved on Day 2. The headache persisted and, on Day 10, the subject was evaluated by CT scan, which showed abnormalities. An event of mild cerebral hemorrhage was reported, which was considered unlikely to be related to study drug. None of these

events was designated as serious by the Investigator. The headache resolved on Day 37.

In the Halflytely treatment group TEAEs reported as severe included single events of ileus, procedural pain, arthropod bite, sinusitis, dizziness, and diverticulum. Each event was considered unrelated or unlikely to be related to study drug, except for the event of dizziness. See Narrative below:

**Subject 212-018**, On study Day 1 a 57-year-old white female experienced severe dizziness no treatment was specified for the event and it was noted as resolved on Study Day 1.

Table 29 Summary of Safety Results (Day Before Dose)

	Study FE2009-02 (Day before dose)	
	PICOPREP N=305	HalfLyteLy N=298
	n (%)	n (%)
Any treatment emergent AE	218 (74)	241 (80)
Any Severe TEAEs	5 (1.7)	6 (2.0)
Serious Adverse Event (SAE)	2 (0.7)	1 (0.3)
Discontinuation due to TEAEs	0	1 (0.3)
Deaths	0	0
Adverse Drug reactions (ADR)	33 (11)	29 (10)

**Reviewer’s Comment:** The treatment emergent adverse events were considered mild to moderate by the Investigators for both treatment regimens. The incidence for both were small and were primarily associated with colonoscopy findings. The adverse drug reactions were typical of the events experienced with the use of osmotic preparations were similar between the two regimens. There were no deaths in either study.

### 7.3.1 Deaths

No patients died during either study.

### 7.3.2 Nonfatal Serious Adverse Events

#### **Study FE2009-01 (Split dose)**

Study FE2009-01 (Split dose) was 4 weeks in duration. During this Study, 1 patient in the PICOPREP treatment group and 2 patients in the HalfLyteLy treatment group experienced SAEs. Details of these serious adverse events are described below.

**Subject 101-125** (PICOPREP), a 56-year-old white female, received her dose of study drug on Day 1 [REDACTED] and colonoscopy was performed the following day (Day 2). On Day 3 [REDACTED], she experienced abdominal pain, was hospitalized, and administered aluminum hydroxide gel with simethicone and hydromorphone for pain and sodium chloride infusion for hydration. Acute pancreatitis of unknown etiology was diagnosed. The subject recovered on Day 8 [REDACTED]. The serious adverse was assessed by the Investigator as severe in intensity and unlikely related to study drug.

**Subject 102-036** (Halflytely), a 63-year-old white female, received her dose of study drug on Day 1 [REDACTED] and colonoscopy was performed the following day (Day 2). Due to colonoscopy findings, the subjects was hospitalized and laparoscopic right hemicolectomy was performed; right-sided colon cancer was diagnosed on Day 14 [REDACTED], with pathology reporting a moderately differentiated adenocarcinoma. The subject recovered on Day 20 [REDACTED]. The Investigator assessed the serious adverse event as severe in intensity and unrelated to study drug.

**Subject 107-019** (HalfLyte), a 51-year-old white male, received his dose of study drug on Day 1 [REDACTED] and colonoscopy was performed the following day (Day 2). On Day 22 [REDACTED], the subject experienced chest pain and was hospitalized for evaluation. Unspecified cardiac enzymes and stress tests were performed and were within normal limits. The subject recovered from the adverse event of non-cardiac chest pain on the same day (Day 22). The Investigator assessed the serious adverse event as mild in intensity and unrelated to study drug.

#### **Study FE2009-02 (Day before dose)**

Study FE2009-02 (Day before dose) was 4 weeks in duration. During this Study, 2 patients in the PICOPREP treatment group and 1 patient in the HalfLyte treatment group experienced SAEs. Details of these serious adverse events are described below.

**Subject 212-014** (PICOPREP), a 57-year-old white female, received her dose of study drug on Day 1 [REDACTED] and colonoscopy was performed the following day (Day 2). During the colonoscopy procedure, biopsy of colonic tissue was performed and results indicated invasive adenocarcinoma (Preferred Term: colon cancer). The subject was scheduled for colon resection on Day 16 [REDACTED], at which time the subject was reported to have recovered with sequelae.

Four days after surgery (Day 20), the subject experienced a rupture of anastomosis (Preferred Term: anastomotic complication); colostomy was performed and the subject recovered the same day (Day 20). On Day 22, the subject developed severe dehydration. She was hospitalized, treated with intravenous fluids and recovered on Day 24. The serious adverse events of colon cancer, anastomotic complication, and

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PICOPREP™ (sodium picosulfate, magnesium oxide and citric acid)

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dehydration were assessed by the Investigator as severe in intensity and unrelated to study drug.

**Subject 212-043** (PICOPREP), a 63-year-old white female, received her dose of study drug on Day 1 [REDACTED] and colonoscopy was performed the following day (Day 2). On Day 13 [REDACTED], the subject experienced an acute coronary syndrome. She was hospitalized for treatment and prescribed sublingual nitroglycerin, acetylsalicylic acid, carvedilol, prasugrel hydrochloride, simvastatin, and valsartan. The subject underwent cardiac catheterization, coronary angioplasty, and coronary stent implantation. She recovered with sequelae on Day 16 [REDACTED]. The Investigator assessed the serious adverse event as severe in intensity and unrelated to study drug.

**Subject 207-056** (HalfLytely), a 58-year-old white male, received his dose of study drug on Day 1 [REDACTED] and colonoscopy was performed the following day (Day 2). During the colonoscopy procedure, severe ileus was diagnosed. The subject was hospitalized and nasogastric decompression was performed. He was treated with ciprofloxacin, metronidazole, enoxaparin sodium, morphine, and pantoprazole and hydrated with half-normal saline and potassium chloride. The subject recovered on Day 5 [REDACTED]. The Investigator assessed the serious adverse event as unlikely related to study drug.

Table 30 Summary of Treatment-Emergent Serious Adverse Events (Safety Analysis Set)

Category System-Organ –Class Preferred Term	PICOPREP N= 601 n (%)	HalfLyteLy N= 600 n (%)
Any treatment emergent serious adverse event	3 (0.6)	3 (0.6)
Cardiac disorders	1 (0.2)	0
Acute coronary syndrome	1 (0.2)	0
GI disorders Pancreatitis, acute ileus	1 (0.2)	1 (0.2)
General disorders/admin site condition	0	1 (0.2)
Non-cardiac chest pain	0	1 (0.2)
Injury, poisoning, procedural complications	0	1 (0.2)
Anastomotic complications	1 (0.2)	0
Metabolism/Nutrition disorders	1 (0.2)	0
Dehydration	1 (0.2)	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (0.2)	1 (0.2)
Colon cancer	1 (0.2)	1 (0.2)

Subjects with multiple events in the same treatment emergent adverse event category are counted only once for the TEAE category.  
Source: Electronically copied and reproduced from Table 9, Summary of Clinical Safety,p.22/77

In Studies FE2009-01 and FE2009-02 combined 3 subjects in the PICOPREP treatment group and 3 subjects in the HalfLyteLy treatment group experienced serious adverse events. All of the serious adverse events were considered severe in intensity, except for 1 event of non-cardiac chest pain that was considered mild. Each SAE was considered unrelated or unlikely to be related to the study drug.

Subjects who experienced treatment –emergent serious adverse events are listed by treatment group in Table 31. These are the same cases described above provided in tabular form.

Table 31 Subjects Who Experienced Treatment –Emergent Serious Adverse Events (Safety Analysis Set)

Study	Subject	Age/ Sex/ Race	Preferred Term	Start Day	Stop Day	Intensity/ Relationship	Outcome
<b>PICOPREP</b>							
FE2009-01	101-125	56/F/ White	Pancreatitis acute	3	8	Severe/ Unlikely	Recovered
FE2009-02	212-014	57/F/ White	Colon cancer	2	16	Severe/ Unrelated	Recovered with sequelae
			Anastomotic complication	20	20	Severe/ Unrelated	Recovered
			Dehydration	22	24	Severe/ Unrelated	Recovered
FE2009-02	212-043	63/F/ White	Acute coronary syndrome	13	16	Severe/ Unrelated	Recovered with sequelae
<b>HalfLytely</b>							
FE2009-01	102-036	63/F/ White	Colon cancer	14	20	Severe/ Unrelated	Recovered
FE2009-01	107-019	51/M/ White	Non-cardiac chest pain	22	22	Mild/ Unrelated	Recovered
FE2009-02	207-056	58/M/ White	Ileus	2	5	Severe/ Unlikely	Recovered

Electronically copied and reproduced from Table 10, Summary of Clinical Safety,p23/77.

An additional PICOPREP subject experienced a SAE following study participation that was not included in the clinical database. The narrative is provided below.

Subject 207-002 was a 74-year-old white female who entered the study with normal liver function test values. A mild elevation in GGT was noted beginning at Visit 3 that continued through Visit 5. At Visit 6, moderate increases in liver function test parameters were noted (ALT: 76 U/L; AST: 56 U/L; alkaline phosphatase: 197 U/L; and GGT: 208 U/L). No relevant medical history or abnormalities on physical examination were reported.

The subject's liver function tests remained moderately elevated over the next few months. Approximately 4 months after study participation, the subject's liver function test values were significantly higher than previous evaluations. Magnetic resonance imaging showed a right hepatic lobe mass and needle biopsy confirmed adenocarcinoma with extensive necrosis.

The serious adverse event of adenocarcinoma of the liver was considered unlikely to be related to study drug.

**Reviewer's comment: The exclusion of this case may be due to the fact that the patient's clinical course continued 4 or months after study participation. Patients were followed for one month. The results may have been made available after the data was locked. The adverse event in this case was not related to the study drug and would have no significant impact on safety analyses.**

### **7.3.3 Dropouts and/or Discontinuations**

In Studies FE2009-01 and FE2009-02 combined 1 subject in the PICOPREP treatment group and 2 subjects in the HalfLyte treatment group were discontinued from the study. Details of these adverse events resulting in discontinuation of the study are described below.

#### **Study FE2009-01 (Split dose)**

**Subject 106-092** (Halflytely), a 66-year-old white female, developed moderate nausea on Day 1 (05 July 2010), while consuming the study drug. Study drug was discontinued and the subject recovered the same day. The subject did not complete the bowel preparation and did not undergo colonoscopy. The Investigator assessed the adverse event as probably related to study drug.

#### **Study FE2009-02 (Day before dose)**

**Subject 204-038** (PICOPREP), a 60-year-old white female, developed mild vomiting on Day 1 [REDACTED] (b) (6) and was unable to complete the required bowel preparation; colonoscopy was not performed. The adverse event of vomiting was assessed by the Investigator as possibly related to study drug; the subject recovered on Day 2. Esophagogastroduodenoscopy with biopsy was performed on Day 2 [REDACTED] (b) (6). Mild gastritis and mild esophagitis were diagnosed, both of which were assessed as unrelated to study drug; omeprazole was prescribed. The subject recovered from the adverse event of gastritis on Day 2 and had not yet recovered from the adverse event of esophagitis at last contact.

**Subject 212-081** (Halflytely), a 31-year-old white female, developed mild vomiting, dizziness, migraine, and syncope on Day 1 (22 August 2010), while consuming the study drug. Study drug was discontinued, the subject was advised to consume solid food, and an unspecified medication was prescribed. The subject recovered from the syncope on Day 1 and from the vomiting, dizziness, and migraine on Day 2 (23 August 2010). The Investigator assessed the adverse events of vomiting, dizziness, and migraine as possibly related and the adverse event of syncope as unlikely related to study drug.

Treatment emergent adverse events for subjects who were discontinued from Studies FE2009-01 and FE2009-02 due to adverse events are listed by treatment group in Table 32.

Table 32 Subjects Who Discontinued From the Study Due to Adverse Events

Study	Subject	Age/ Sex/Race	Preferred Term	Start Day	Stop Day	Intensity/ Relationship	Outcome
PICOPREP							
FE2009-02	204-038	60/F/White	Vomiting	1	2	Mild/ Possible	Recovered
			Gastritis	2	2	Mild/ Unrelated	Not yet
			Esophagitis	2	Ongoing	Mild/ Unrelated	recovered
HalfLytely							
FE2009-01	106-092	66/F/White	Nausea	1	1	Moderate/ Probable	Recovered
FE2009-02	212-081	31/F/White	Vomiting	1	2	Mild/ Possible	Recovered
			Dizziness	1	2	Mild/ Possible	Recovered
			Migraine	1	2	Mild/ Possible	Recovered
			Syncope	1	1	Mild/ Unlikely	Recovered

Electronically copied and reproduced from Table 12, Summary of Clinical Safety, p.25/77.

### .3.4 Significant Adverse Events

#### Treatment Emergent Adverse Events by Dosing Regimen

The incidence of TEAEs was similar between the Split dose and Day before dosing regimens (69% and 73.6% respectively). No differences were observed between the dosing regimens with respect to any specific TEAE.

Table 33 Treatment –Emergent Adverse Events Experienced by >2.0% of Subjects in Either PICOPREP dosing Regimen(Split-dose and Day-before)

Category System -Organ-Class Preferred Term	PICOPREP n(%)	
	Split-Dose N=305	Day-Before N=296
Any treatment-emergent adverse event	211 (69.2)	218 (73.6)
Gastrointestinal disorders	162(53.1)	183(61.8)
Haemorrhoids	54 (17.7)	85 (28.7)
Diverticulum	60 (19.7)	63 (21.3)
Colonic polyp	52 (17.0)	37 (12.5)
Diverticulum intestinal	11 (3.6)	27(9.1)
Nausea	15(4.9)	11 (3.7)
Rectal polyp	12 (3.9)	13(4.4)
Polyp colorectal	9 (3.0)	3 (1.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	62 (20.3)	53 (17.9)
Colon adenoma	56 (18.4)	47 (15.9)
Rectal adenoma	7 (2.3)	5 (1.7)
Nervous system disorders	16 (5.2)	16 (5.4)
Headache	13(4.3)	10 (3.4)

Subjects with multiple events in the same TEAE category are counted only once for the TEAE category.  
Electronically copied and reproduced , Table 7, Summary of Clinical Safety,p .21/77.

#### Drug Related Treatment-Emergent Adverse Events By Dosing Regimen

The Incidence of TEAEs considered possibly or probably related to the study drug was slightly higher in the Day-before dosing regimen compared to the Split-dose dosing regimen (11.1% compared to 6.2%). Drug related TEAEs reported by >1% of subjects in either treatment group were nausea, vomiting, and headache.

Table 34 Drug-Related Treatment-Emergent Adverse Events Experienced by>1.0% of Subjects in Either PICOPREP Dosing Regimen (Split-Dose and Day-Before)

Category System -Organ-Class Preferred Term	PICOPREP n(%)	
	Split-Dose N=305	Day-Before N=296
Any drug-related• treatment-emergent adverse event	19 (6.2)	33(11.1)
Gastrointestinal disorders	10 (3.3)	18(6.1)
Nausea	8 (2.6)	9 (3.0)
Vomiting	3 (1.0)	4 (1.4)
Nervous system disorders	5 (1.6)	8 (2.7)
Headache	5 (1.6)	8 (2.7)

Subjects with multiple events in the same TEAE category are counted only once for the TEAE category.  
a. Possible or probable relationship, assessed by the investigator, or records where relationship was missing.  
Electronically reproduced and copied , Table 8, Summary of Clinical Safety,p.22/77.

### **7.3.5 Submission Specific Primary Safety Concerns**

A review of safety information from clinical trial and postmarketing use of PICOPREP in adults has not prompted any submission-specific safety concerns. The adverse events described are consistent with those previously described and labeled in other approved osmotic bowel cleansing agents.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

The most common adverse events for the combined Studies FE2009-01 and FE2009-02 reported in  $\geq 2\%$  of subjects were colonoscopy related findings that included hemorrhoids, diverticuluae, colon adenomas and colon polyps. See Table 26 in Section 7.1.3.

### **7.4.2 Laboratory Findings**

#### **Study FE2009-01(Split dose)**

##### **Mean Changes**

**Hematology** The mean changes from baseline to Visits 3,4,5,and 6 in hematology and coagulation values were small with no trends observed between subjects who received PICOPREP or HalfLyte. This was also true for mean changes from baseline to Visits 3,4,5,and 6 in neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

##### **Clinical Chemistry.**

A small mean increase in magnesium was observed at Visit 3 in the PICOPREP treatment group that was not observed in the HalfLyte treatment group. This finding is not unexpected given the magnesium component of PICOPREP product. Small mean decreases were observed for other chemistry values such as sodium, and potassium. No discernable trends were observed between subjects who received PICOPREP or HalfLyte.

##### **Urinalysis.**

Mean changes from baseline to Visits 3,4,5,and 6 in urinalysis values were small and no trends were observed between the 2 treatment groups

### Shift Analysis

Shifts from normal chemistry values at baseline to outside the normal range at Visit 3 were observed in both the PICOPREP and HalfLyte treatment groups. The majority of shifts occurred in ≤5% of subjects.

Compared to subjects who received HalfLyte more subjects receiving PICOPREP developed Increases in albumin values and decreases in urea values at Visit 3 (8.8% vs 4.2%) and (20.9% vs 12%) respectively.

More PICOPREP subjects developed decreases in sodium, potassium and chloride than HalfLyte. The number of patients with total bilirubin values above the normal range were similar between the treatment groups; 12% PICOPREP and 14% HalfLyte.

Shifts from normal ALT values at baseline to above normal range were higher among PICOPREP subjects compared to HalfLyte subjects at Visit 3 (3.3% vs. 1.8%), 4 (3.2% vs. 0.7%), 5 (3.2% vs. 1.8%), and 6 (2.2% vs. 1.1%). This trend was also observed for AST values at Visits 3 (5.9% vs. 3.4%) and 4 (3.6% vs. 0.7%), but the incidences were similar between the treatment groups at Visits 5 (2.5% vs. 2.2%) and 6 (2.2% vs. 1.8%).

The proportion of patients who shifted from normal creatinine clearance values at baseline to below normal range at each visit 7% to 14% in the PICOPREP treatment group and from 8% to 10% in the HalfLyte treatment group.

The proportions of subjects who shifted from normal creatinine values at baseline to above the normal range at each visit ranged from 2% to 7% in the PICOPREP treatment group and from 4% to 5% in the HalfLyte treatment group.

Table 35 Shifts from Normal Baseline to Outside the Normal Range at Visits 3, 4, and 5 in Chemistry Values (Safety Analysis Set)

Variable	PICOPREP, n (%)			HalfLyte, n (%) N= 298		
	Visit 3	Visit 4	Visit 5	Visit 3	Visit 4	Visit 5
ALT (U/L)	(N275)	(N278)	(N279)	(N281)	(N279)	(N 280)
Above ULN	9 (3.3)	9 (3.2)	9 (3.2)	5 (1.8)	2 (0.7)	5(1.8)
AST (U/L)	(N255)	(N276)	(N278)	(N265)	(N276)	(N276)
AboveULN	15 (5.9)	10 (3.6)	7 (2.5)	9 (3.4)	2 (0.7)	6 (2.2)
Albumin (g/L)	(N294)	(N295)	(N296)	(N289)	(N286)	(N286)
BelowLLN	2 (0.7)	3 (1.0)	1 (0.3)	1 (0.3)	0	1 (0.3)
Above ULN	26 (8.8)	3(1.0)	4 (1.4)	12(4.2)	1 (0.3)	3 (1.0)
Alkaline phosphatase (U/L)	(N263)	(N285)	(N287)	(N268)	(N 281)	(N 281)
BelowLLN	2 (0.8)	2 (0.7)	1 (0.3)	3 (1.1)	2 (0.7)	2(0.7)
Above ULN	2 (0.8)	0	0	2 (0.7)	2 (0.7)	3 (1.1)

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Bilirubin	(N296)	(N298)	(N299)	(N293)	(N292)	(N292)
Above ULN	36 (12.2)	7 (2.3)	4 (1.3)	41 (14.0)	2 (0.7)	0
Calcium (mmno/L)	(N- 292)	(N- 292)	(N- 293)	(N- 286)	(N- 283)	(N- 283)
BelowLLN	2 (0.7)	0	0	1 (0.3)	1 (0.4)	1 (0.4)
Above ULN	4 (14)	2 (0.7)	5 (17)	6 (2.1)	5 (1.8)	3 (1.1)
Chloride (mmno/L)	(N- 301)	(N- 302)	(N- 303)	(N- 298)	(N- 295)	(N- 295)
BelowLLN	11 (3.7)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.7)	3(1.0)
Creatinine clearance (rnL/rnin)	(N221)	(N223)	(N223)	(N214)	(N 212)	(N 213)
BelowLLN	22 (10.0)	32 (14.3)	22 (9.9)	17 (7.9)	22 (10.4)	17 (8.0)
Creatinine enzymatic	(N- 260)	(N- 264)	(N- 264)	(N- 268)	(N- 267)	(N- 267)
BelowLLN	2 (0.8)	2 (0.8)	1 (0.4)	2 (0.7)	1 (0.4)	0
Above ULN	5 (19)	18 (6.8)	10 (3.8)	13(4.9)	11 (4.1)	13 (4.9)
GGT (U/L)	(N- 251)	(N- 252)	(N- 253)	(N- 255)	(N- 252)	(N- 253)
Above ULN	6(2.4)	6(2.4)	7 (2.8)	5(2.0)	1 (0.4)	2 (0.8)
Glucose (mmnoL)	(N268)	(N270)	(N270)	(N266)	(N263)	(N264)
BelowLLN	6(2.2)	4 (1.5)	6 (2.2)	11(4.1)	15 (5.7)	10 (3.8)
Above ULN	6(2.2)	20 (7.4)	17 (6.3)	7 (2.6)	20 (7.6)	15 (5.7)
Potassium (mmno/L)	(N260)	(N282)	(N285)	(N268)	(N279)	(N279)
BelowLLN	19 (7.3)	15 (5.3)	11 (3.9)	11(4.1)	10 (3.6)	8 (2.9)
Above ULN	7 (2.7)	4(1.4)	5(1.8)	5(1.9)	1 (0.4)	8 (2.9)
Magnesium (mmno/L)	(N294)	(N296)	(N297)	(N294)	(N 291)	(N 291)
BelowLLN	0	2 (0.7)	4 (1.3)	0	2 (0.7)	0
Above ULN	34(11.6)	0	0	0	0	1 (0.3)
Protein (g/L)	(N289)	(N 291)	(N292)	(N290)	(N287)	(N287)
BelowLLN	0	1 (0.3)	3 (1.0)	1 (0.3)	2 (0.7)	2(0.7)
Above ULN	10 (3.5)	1 (0.3)	3 (1.0)	8 (2.8)	1 (0.3)	1 (0.3)
Sodium (mmno/L)	(N- 298)	(N- 299)	(N- 300)	(N- 295)	(N- 292)	(N- 292)
BelowLLN	11 (3.7)	4 (1.3)	2(0.7)	3(1.0)	5(1.7)	1 (0.3)
Above ULN	0	0	1 (0.3)	2 (0.7)	0	1 (0.3)
Urea mmo/L)	(N- 287)	(N- 287)	(N- 288)	(N- 276)	(N- 274)	(N- 274)
(BelowLLN	60 (20.9)	12 (4.2)	13 (4.5)	33 (12.0)	6 (2.2)	4 (1.5)
Above ULN	0	4 (14)	4(1.4)	0	3(1.1)	7 (2.6)

Electronically copied and reproduced from Table 10-9;CSR FE2009-01 p.68/80

**Reviewer's Comment: A statistically significant greater percentage of patients that received PICOPREP had an albumin value outside the normal range at Visit 3. The clinical correlate to this is unclear. By Visit 4 there were considerably less abnormal values for PICOPREP suggesting that the occurrence does not indicate a trend or an emerging safety signal.**

**Transient elevations of AST and ALT may occur clinically. Non persistent elevations of these liver associated enzymes would suggest that the initial elevations were not clinically significant.**

**Of the 601 patients studied in the PICOPREP treatment group, 489 subjects were ≤ 65 years of age and 112 subjects were ≥ 65 years. Shifts from baseline to below**

**normal range in creatinine clearance may be related to the age of the population studied.**

## **Clinically Significant Abnormalities**

### **Clinical Chemistry**

Few subjects met criteria for markedly abnormal chemistry values. The proportions of subjects who met the criteria for markedly abnormal chemistry values were similar between the treatment groups. The incidence of increased magnesium values in the PICOPREP treated subjects was the exception. Large proportions of subjects with decreased creatinine clearance were similar between the treatment groups PICOPREP 31% and HalfLyte 32%. For the majority of parameters in both treatment groups, the incidence of markedly abnormal values was  $\leq 1\%$ .

### **Study FE2009-02(Day before Dose)**

#### Mean changes

**Hematology** The mean changes from baseline to Visits 3,4,5,and 6 in hematology and coagulation values were small with no trends observed between subjects who received PICOPREP or HalfLyte. This was also true for mean changes from baseline to Visits 3,4,5,and 6 in neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

**Clinical Chemistry.** A small mean increase in magnesium was observed at Visit 3 in the PICOPREP treatment group that was not observed in the HalfLyte treatment group. This finding is not unexpected given the magnesium component of PICOPREP product. Small mean decreases were observed for other chemistry values such as sodium, and potassium. No discernable trends were observed between subjects who received PICOPREP or HalfLyte.

**Urinalysis.** Mean changes from baseline to Visits 3,4,5,and 6 in urinalysis values were small and no trends were observed between the 2 treatment groups

#### Shift Analysis

Shifts from normal chemistry values at baseline to outside the normal range at Visit 3 were observed in both the PICOPREP and HalfLyte treatment groups. The majority of shifts occurred in  $\leq 5\%$  of subjects.

Compared to subjects who received HalfLyte more subjects receiving PICOPREP developed increases in albumin values and decreases in urea values at Visit 3 (5.8% vs 2.1%) and (16.9% vs 14%) respectively.

The number of patients with total bilirubin values above the normal range were similar between the treatment groups ; 9% PICOPREP and 8% HalfLyte.

As expected, the incidence of increased magnesium was higher in the PICOPREP treatment group compared to the HalfLyte treatment group 9% vs 0.3% respectively at Visit 3. By Visit 4, the proportion of patients with abnormal magnesium values decreased and was comparable between the treatment groups at Visits 4,5, and 6.

Shifts from normal ALT values at baseline to above normal range were higher among PICOPREP subjects compared to HalfLyte subjects at Visit 3 (7% vs. 4%). At Visits 4,5,and 6 the proportions of subjects with AST values above the normal range were similar between the treatment groups.

The proportion of patients who shifted from normal creatinine clearance values at baseline to below normal range at each visit 6% to 13% in the PICOPREP treatment group and from 4% to 6% in the HalfLyte treatment group.

The proportions of subjects who shifted from normal creatinine values at baseline to above the normal range at each visit ranged from 4% to 7% in the PICOPREP treatment group and from 4.% to 5% in the HalfLyte treatment group.

Table 36 Shifts from Normal Baseline to Outside the Normal Range at Visits 3, 4,and 5 in Chemistry Values (Safety Analysis Set)

Variable	PICOPREP, n(%) N =296			HalfLyte, n (%) N= 302		
	Visit 3	Visit 4	Visit 5	Visit 3	Visit 4	Visit 5
ALT (U/L)	(N = 271)	(N = 269)	(N = 269)	(N = 277)	(N = 275)	(N = 276)
Above ULN	10 (3.7)	10 (3.7)	3 (1.1)	9 (3.2)	7 (2.5)	10 (3.6)
AST (U/L)	(N = 272)	(N = 273)	(N = 273)	(N = 265)	(N = 271)	(N = 271)
Above ULN	19 (7.0)	8 (2.9)	2 (0.7)	10 (3.8)	11 (4.1)	4 (1.5)
Albumin (g/L)	(N = 277)	(N = 275)	(N = 275)	(N = 283)	(N = 279)	(N = 279)
BelowLLN	0	0	0	2 (0.7)	1 (0.4)	0
Above ULN	16 (5.8)	2 (0.7)	2 (0.7)	6 (2.1)	2 (0.7)	7 (2.5)
Alkaline phosphatase (U/L)	(N = 276)	(N = 278)	(N = 277)	(N = 276)	(N = 283)	(N = 283)
BelowLLN	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	1 (0.4)	4 (1.4)
Above ULN	0	0	1 (0.4)	1 (0.4)	1 (0.4)	0
Bilirubin	(N = 281)	(N = 280)	(N = 279)	(N = 289)	(N = 287)	(N = 288)
Above ULN	24 (8.5)	2 (0.7)	1 (0.4)	23 (8.0)	1 (0.3)	0
Calcium	(N = 276)	(N = 274)	(N = 274)	(N = 282)	(N = 278)	(N = 278)
BelowLLN	0	2 (0.7)	0	2 (0.7)	1 (0.4)	0
Above ULN	9 (3.3)	4 (1.5)	3 (1.1)	6 (2.1)	6 (2.2)	4 (1.4)
Chloride (mmo/L)	(N = 287)	(N = 285)	(N = 285)	(N = 297)	(N = 293)	(N = 293)
BelowLLN	3 (1.0)	1 (0.4)	0	0	0	0
Creatinine clearance (mL/min)"	(N = 199)	(N = 198)	(N = 198)	(N = 224)	(N = 220)	(N = 219)
BelowLLN	26(13.1)	25 (12.6)	11 (5.6)	25 (11.2)	27 (12.3)	28 (12.8)
Creatinine enzymatic (mmo/L)	(N = 266)	(N = 263)	(N = 264)	(N = 270)	(N = 266)	(N = 265)
BelowLLN	2 (0.8)	0	3 (1.1)	2 (0.7)	1 (0.4)	2 (0.8)
Above ULN	12 (4.5)	19 (7.2)	10 (3.8)	16 (5.9)	15 (5.6)	10 (3.8)

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GGT (U/L)	(N = 245)	(N = 242)	(N = 241)	(N = 244)	(N = 239)	(N = 240)
Above ULN	11 (4.5)	10 (4.1)	7 (2.9)	4 (1.6)	3 (1.3)	4 (1.7)
Glucose (mmo/L)	(N = 260)	(N = 258)	(N = 258)	(N = 273)	(N = 270)	(N = 270)
BelowLLN	6 (2.3)	12 (4.7)	9 (3.5)	13 (4.8)	5 (1.9)	10 (3.7)
Above ULN	12 (4.6)	11 (4.3)	13 (5.0)	8 (2.9)	10 (3.7)	14 (5.2)
Potassium (mmo/L)	(N = 274)	(N = 276)	(N = 276)	(N = 271)	(N = 277)	(N = 278)
BelowLLN	13 (4.7)	8 (2.9)	6 (2.2)	13 (4.8)	9 (3.2)	14 (5.0)
Above ULN	0	1 (0.4)	2 (0.7)	1 (0.4)	0	0
Magnesium (mmo/L)	(N = 288)	(N = 286)	(N = 286)	(N = 289)	(N = 285)	(N = 285)
BelowLLN	0	4 (1.4)	10 (3.5)	3 (1.0)	4 (1.4)	4 (1.4)
Above ULN	25 (8.7)	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.4)
Protein (g/L)	(N = 286)	(N = 283)	(N = 283)	(N = 293)	(N = 289)	(N = 289)
BelowLLN	1 (0.3)	1 (0.4)	1 (0.4)	5 (1.7)	5 (1.7)	4 (1.4)
Above ULN	5 (1.7)	2 (0.7)	2 (0.7)	4 (1.4)	0	2 (0.7)
Sodium (mmo/L)	(N = 286)	(N = 284)	(N = 285)	(N = 295)	(N = 291)	(N = 291)
BelowLLN	3 (1.0)	4 (1.4)	1 (0.4)	3 (1.0)	1 (0.3)	1 (0.3)
Urea (mmo/L)	(N = 267)	(N = 263)	(N = 265)	(N = 274)	(N = 269)	(N = 269)
BelowLLN	45 (16.9)	14 (5.3)	5 (1.9)	37 (13.5)	7 (2.6)	5 (1.9)
Above ULN	1 (0.4)	4 (1.5)	7 (2.6)	2 (0.7)	4 (1.5)	6 (2.2)

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**Reviewer's Comment:**

The albumin values were not significantly elevated in the PICOPREP treatment group compared to the HalfLyte treatment group in the day before dosing regimen as it was for the split dose. The elevations were not persistent throughout the Visits suggesting their occurrence has little clinical significance. ALT values were elevated at the first Visit (Visit 3) but the number of patients with elevated ALT was similar for the 2 treatment groups at subsequent visits. These shifts do not appear to be indicative of any clinically significant event.

The shifts in creatinine clearance may be related to the age of the study population.

In the day before dose study there appeared to be no increased number of PICOPREP subjects with decreased sodium, potassium and chloride values as was observed with the split dose regimen. The decrease in these electrolyte values was extremely minimal and would most likely not manifest clinically as an adverse event. Additionally, the number of patients affected was low and would likely not signal a trend. Transient decreases in electrolytes are consistent with a class effect for osmotic bowel preparations. In most patients, adequate fluid replacement is sufficient to result in normalization of these values. Those patients with a history of impaired cardiac or renal function who may be clinically more susceptible to even minimal shifts in fluid status or electrolytes may benefit from electrolyte monitoring before and after colon preparation and colonoscopy.

**Additionally, a sub-analysis was conducted per a request for information to the sponsor. The sponsor provided a tabulation of frequency of all adverse events (AEs) (including serious adverse events [SAEs]), by treatment arm, that occurred on or past the first day of the study drug administration through visit 6. The following subjects were included: Subjects who had normal potassium levels at baseline and below the normal range on the day of colonoscopy (Visit3). Other electrolytes such as sodium, chloride and calcium were also reviewed in this manner. The adverse events observed in the electrolyte abnormality groups ie sodium were consistent with the events observed in general. Again, the AEs were primarily the result of findings on colonoscopic examination. No particular safety signals emerged. The number of events other than colonoscopic findings were extremely small in number.**

**Subjects who had normal magnesium levels at baseline and above the normal range on the day of colonoscopy were reviewed. No significant adverse event profile emerged suggesting a safety signal. This was consistent observed in subjects with normal creatinine levels at baseline and above the normal range on the day of colonoscopy as well.**

**The sponsor was asked to perform the same analysis for SAEs. None of the electrolyte cohorts showed a serious adverse event except for magnesium where one subject developed acute pancreatitis. This SAE is discussed previously in Section 7.3.2 of the review. The investigator reported this event as unlikely related to the drug.**

**Overall, the adverse events that were not endoscopic findings occurred rarely and did not indicate new safety signals.**

#### **7.4.3 Vital Signs**

##### **Studies FE2009-01 (Split dose) and FE2009-02 (Day before dose)**

Vital sign trends, individually clinical significant abnormalities, and changes over time were reviewed. No clinically important findings were seen.

#### **7.4.4 Electrocardiograms (ECGs)**

##### **Studies FE2009-01(Split dose) and Study FE2009-02 (Day before dose)**

ECG data showed no significant change in heart rate. There was no signal of any effect of PICOPREP on AV conduction or cardiac depolarization as measured by the PR and QRS interval durations. There was no significant effect of PICOPREP on cardiac repolarization, as measured by the lack of a significant change in QTcF. The lack of

change in QTcF is not a TQT and there is no positive control. No new clinically relevant morphological changes were observed.

**Reviewer's comment: The Division requested the Applicant provide a thorough QT study. The study has not been submitted at the time of this review.**

#### **7.4.5 Special Safety Studies/Clinical Trials**

No special safety studies or clinical trials were submitted in support of this application.

#### **7.4.6 Immunogenicity**

Not applicable. The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

Not applicable. All patients were treated with PICOPREP 2 pouches either as a split dose (2 day) dosing regimen or a day before dosing regimen.

#### **7.5.2 Time Dependency for Adverse Events**

No particular explorations for time dependency of adverse events were conducted.

#### **7.5.3 Drug-Demographic Interactions**

Subgroup analyses of AE data for gender and race.

#### **7.5.4 Drug-Disease Interactions**

Renal impairment

In patients with severely reduced renal function, accumulation of magnesium in plasma may occur. This should be taken into consideration when prescribing PICOPREP for patients with reduced kidney function or patients on a controlled potassium diet. In the Phase 3 trials, however, with over 370 patients enrolled with mild to moderate renal impairment at screening (creatinine clearance <90 mL/min by Cockcroft-Gault

estimation), no clinically significant events resulted with regards to low serum potassium.

#### Inflammatory Bowel Disease

PICOPREP use may exacerbate inflammatory bowel disease and result in transient ileal aphthous ulcers. Occurrence of these events has been observed as a possible class event with the use of osmotic bowel cleansing preparations, PICOPREP should not be used in suspected toxic dilation of the colon.

#### Gastrointestinal Complications

PICOPREP is a potent stimulant cathartic and osmotic laxative that acts locally in the colon. As such, PICOPREP treatment is contraindicated in patients with gastrointestinal obstruction, bowel perforation, toxic colitis or toxic megacolon, gastric retention, and ileus.

#### Electrolyte Abnormalities

Colon cleansing may result in dehydration, especially in special populations such as the elderly and pediatrics. Patients with cardiac disease or renal insufficiency may be vulnerable to the hemodynamic changes that occur with dehydration in addition to electrolyte aberrations. PICOPREP use has been shown to result in an increase in serum magnesium, and reductions in concentrations of serum urea, sodium, and potassium.

Hyponatremia, a potentially life-threatening condition particularly in the elderly and infirm, can occur following the use of a bowel-cleansing agent with inadequate or inappropriate fluid and electrolyte repletion. The condition is often associated with vomiting and/or diarrhea, which may exacerbate loss of fluid and salts. Adequate hydration must be maintained in all patients to minimize the risk of developing hyponatremia.

### **7.5.5 Drug-Drug Interactions**

No formal clinical drug-interaction studies have been conducted with PICOPREP.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

Studies including Ames assay, a mouse lymphoma assay and a micronucleus assay conducted in mice have shown no mutagenic potential of PICOPREP. Due to the very

short treatment duration, no long term studies in animals have been performed to evaluate the carcinogenic potential of PICOPREP.

### 7.6.2 Human Reproduction and Pregnancy Data

Clinical experience of the use of PICOPREP during pregnancy is limited and therefore, caution should be observed, particularly during the first trimester. Neither sodium picosulfate nor magnesium citrate has been shown to be excreted in breast milk.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant submitted a request to defer the conduct of pediatric assessments of safety and efficacy of PICOPREP in children from ages (b) (4) until the product is approved for use in adults (b) (4).

The deferred pediatric studies will be conducted in 2 parts as outlined below:

Study 1: Multicenter, open label, safety and efficacy assessment of PICOPREP in children ages 9 – 16.

- a. Children ages 9 – 16, treated with PICOPREP, undergoing elective colonoscopy
  - b. Primary Efficacy Endpoint: Aronchick Scale (efficacy) and Safety
  - c. Secondary Efficacy Endpoint: Ottawa Scale
- Protocol submission: February 2013 (assumes July 2012 approval for adults)
  - Study completion: July 2015
  - Submission of study report: January 2016

Study 2: Multicenter, open label, safety and efficacy assessment of PICOPREP in children ages 2 to <9

- a. Children ages 2 to <9, treated with PICOPREP, undergoing elective colonoscopy
  - b. Primary Efficacy Endpoint: Aronchick Scale (efficacy) and Safety
  - c. Secondary Efficacy Endpoint: Ottawa Scale
- Protocol submission: February 2016
  - Study completion: July 2018
  - Submission of study report: January 2019

Dosing:

The proposed study designs are intended to provide adequate safety and efficacy information for the age groups to guide clinical care and to support labeling. The PICOPREP formulation was approved for pediatric dosing in the UK (Picolax) in 1985, and in Canada (Pico-Salax) in 2004.

The Canadian label provides specific dosing by age group that Ferring intends to use as a basis for dosing in the U.S. PICOPREP pediatric trials (outlined below):

2 to <6 years old:

One day before your procedure: Take  $\frac{1}{4}$  of the prepared solution as per DOSING INSTRUCTIONS (first dose) at 6:00 pm followed by one cup of clear liquid (250 mL, 8 oz) every hour while the child is awake. No solid food should be taken after 6:00 pm.

On the same day as your procedure: Take  $\frac{1}{4}$  of the prepared solution as per DOSING INSTRUCTIONS (second dose) at 8:00 am, followed by one cup of clear liquid (250 mL, 8 oz) every hour up to 2 hours prior to your child's procedure.

6 to 12 years old:

One day before your procedure: Take  $\frac{1}{2}$  of the prepared solution as per DOSING INSTRUCTIONS (first dose) at 6:00 pm followed by one cup of clear liquid (250 mL, 8 oz) every hour while the child is awake. No solid food should be taken after 6:00 pm.

On the same day as your procedure: Take  $\frac{1}{2}$  of the prepared solution as per DOSING INSTRUCTIONS (second dose) followed by one cup of clear liquid (250 mL, 8 oz) every hour up to 2 hours prior to your child's procedure.

>12 years:

Split-dose dosing as for adults.

**Reviewer's Comment: A partial waiver for patients less than 6 months is reasonable, as bowel preparation can be achieved in infants <6 months with only administration of clear liquids for 24 hours and the NuLytely comparator is approved down to 6 months of age. It is unlikely that PICOPREP will be used in a substantial number of patients in this age group. In addition to the Applicant's 2 proposed pediatric studies, the division is recommending that the Applicant conduct a study in children, ages 6 months to <2 years undergoing elective colonoscopy.**

A Request for Information was sent to the Applicant 01May2012 requesting an explanation for how the pediatric doses of the products approved in Canada and the United Kingdom were established. The following is a summary of the response.

In 1980 when PICOPREP was first approved the pediatric dosing was based on a study by Dr. J Ratcliffe, a consultant Pediatric Radiologist Department of

Radiodiagnosis, Booth Hall Children's Hospital, Manchester, UK). During the Mutual Recognition Procedure completed April 2010, the product (including the pediatric posology) was also approved in the participating 24 European Economic Area countries. The approval was granted on the basis of EU directive 2001/83/EC, article 10a "well-established use". Under this paragraph the following applies:

*Article 10a*

*(...) the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature.*

No further studies were required for the MRP in EU since the drug substance had been sold in an EU country for at least 10 years, and because the available literature provided the necessary level of evidence that the product has a recognized efficacy and an acceptable level of safety. In granting the approval in 2010, the National Competent Authorities recognized that no additional pediatric studies were necessary to justify dosing.

The Canadian label (at the time of approval) generally followed the UK label, with some adjustments to comply with labeling standards for bisacodyl and other stimulant laxatives.

These standards stipulated 5 mg bisacodyl for children 6-12 years, and "consult physician" for children below 6 years of age. On the basis of this, Pico-Salax was approved for pediatric dosing at the equivalent of 5 mg (ages 6-12) and 2.5 mg (under age 6) of sodium picosulfate.

Subsequent to the Canadian approval, Turner and colleagues confirmed the Canadian pediatric dosing within the label by conducting a large well-controlled randomized clinical study of 89 pediatric patients ages 4 – 18 years comparing Pico-Salax to that of PEG-ELS for colonoscopy Cleansing [Turner D, et al., *Pico-Salax versus polyethylene glycol for bowel cleanout before colonoscopy in children: a randomized controlled trial. Endoscopy 2009;41:1038–45*. This study was conducted at the Toronto University Hospital for Sick Children.

The Turner study was powered to detect a difference in satisfaction using a Likert scale, however, effectiveness of bowel cleansing was also assessed with no difference found between Pico-Salax and PEG-ELS. PICOPREP was found to be better tolerated than PEG-ELS.

**Reviewer's Comment: Based on the dosing rationale provided by the Canadian approval, the doses seem appropriate and further dose ranging studies may be impractical especially in the younger children, 6 months to <2 years and 2 years to <9.**

#### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

No cases of overdose were reported in the PICOPREP clinical program. It is likely that overdosage would lead to profuse diarrhea and treatment for overdose would consist of general supportive measures and maintenance of fluid intake. A patient who has taken an overdose should be monitored carefully, and treated symptomatically for complications.

There is no known potential for abuse with PICOPREP. Withdrawal and Rebound are not applicable.

#### **7.7 Additional Submissions / Safety Issues**

The most recent safety update for PICOPREP was submitted January 20, 2012 as a principle line listing of all reportable events involving the PICOPREP formulation as it is distributed outside the United States. The report dates are 01-Jan-2011 to 31-Dec-2011. The Product is also known under the names PICOLAX and PICOSALAX, with a related formulation Cilaxoral. The sources of these reports include clinical trial, spontaneous, literature and regulatory reports.

The most common reactions for Metabolic and Nutrition disorders include electrolyte abnormalities such as hyponatremia and hypokalemia. Nervous system disorders were associated with reported seizures (convulsions). Seizures were thought to be related to hypovolemia and hyponatremia in these patients. Other reported neurologic findings such as cerebral edema, loss of consciousness and coma were invariably associated with hyponatremia. There were 2 pediatric reports of seizure with the use of Picosalax.

There was one case of ischemic colitis reported in a male. Additional medical information was not included. The indication for use of the Picolax and the amount of drug ingested is unknown. There was 1 report of exacerbation of Crohn's disease and a report of aphthous ileal ulcers. These events occur rarely but are recognized class related adverse events with the use of osmotic bowel cleansing preparations.

**Metabolism and Nutrition disorders**

Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
DE006533	F/49	Electrolyte Imbalance	26-Jul-2011	Picolax	Recovered	Colonoscopy
IL-004497	F/65	Hypocalcemia	1-Jan-2011 to 2-Jan-2011	Picolax 2 sachets	Recovered	Bowel cleaning

**Psychiatric disorders**

Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
DE004400	F/55	Delirium	15-16Dec-2010	Picolax 2 sachets	Recovered	Colonoscopy
DE006421	F/64	Anxiety	14-15-DEC-2010	Picolax 2 sachets	Recovered	Colonoscopy

**Nervous system disorders**

Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
CA004376	M/74	Seizure	unk	Picolax 2 sachets	Recovered	Bowel cleans prior to Xray
Pt received multiple concomitant meds and limited info regarding dose and indication						
CA004377	F/39	Seizure	15Aug2010	Picolax	Unk	Colonoscopy
Medical history of nocturnal seizures						
CA004565	F/12	Seizure	2 days	½ sachet x2	Recovered	Colonoscopy
Reported in LIT; Turner et al Pico-Salax versus polyethylene glycol for bowel cleanout before colonoscopy in children: a randomized controlled trial. Endoscopy 2009;41(12);1038-45						

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Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
DE004684	F/59	Presyncope	24-25- Jan2011	Picolax 2 sachets	Recovered	Colonoscopy
DE005111	F/63	Seizure	13- 14Jan2011	Picolax 2 sachets	Recovering	Colonoscopy
DE006101	M/70	LOC	Unk	Picolax	Recovered	Colonoscopy
Epilepsy, hyponatremia, and hypervolemia						
DE006871	F/78	Cerebral edema	9- 10Nov2010	Picolax	Recovered	Colonoscopy
Suspected concomitant meds HCTZ /losartan; pt drank 2L liquid w/in 2 hrs after prep						
DE007203	F/5	Seizure	9- 10Nov2011	Picolax	Recovered	Colonoscopy
Seizure thought likely due to hyponatremia						
FR006174	F/55	Coma	Unk	2 sachets	Recovered	Colonoscopy
Hyponatremia which led to confusion coma and cerebral infarct may have been caused by excessive fluid intake; possible causal relationship between the events and PICOPREP						
FR006555	F/35	Vasovagal/syncope	Unk	Picolax	Unk	Reporter causality implied
NL007073	F/unk	Fainted (Syncope)	Unk	150ml	Recovered	Colonoscopy

#### Eye disorders

Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
DE005729	F/69	Visual disturbances	24-May- 2011	Picolax bid	Recovered	Unknown

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**Vascular disorders**

Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
DE006218	F/50	Circulatory Collapse	Unknown	Picolax	Recovered	Colonoscopy
Pts complaints incl. HA, N/V,LOC; AEs resolved after head massage and soup. Not seen by MD at the time of events						
FR005473	M/Unk	Vasovagal malaise	Unk	Picolax	Recovered	Colonoscopy
<b>Respiratory, thoracic and mediastinal disorders</b>						
CA006412	F/57	Burning in throat	21-Sept-2011	2 sips	Recovered	Colonoscopy

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**Gastrointestinal disorders**

Case #	Sex/Age	Reaction MedDRA PT	Treatment Date	Dose	Outcome	Indication
CA005236	M/Unk	Ischemic colitis	Unknown	Picolax	Unknown	Unknown
DE0049026421	F/74	Vomiting	Unknown	1 sachet at 3pm and 1 sachet at 6pm	Recovered	Colonoscopy
Vomiting HA, and Hyponatremia						
FR005873	F/51	Vomiting	27-28Jun2011	Picolax	Recovering	Colonoscopy
Erythema and Petechiae						
FR006799	F/33	Crohns Disease aggravated	Unknown	Picolax 2 sachets	Unknown	Colonoscopy
Causality implied, mild aphthoid ileal ulcers reported and listed in the Core Safety Profile						
SE006588	M/60	Constipation	12-25Jul2011	Cilaxoral	Fatal	Constipation
Portal vein thrombosis, Ascites, Hematuria, Pancreatitis, PE, Sudden cardiac death						
DE004505	F/75	Rhabdomyolysis	Sep 2010	Picolax	Recovering	Colonoscopy
Rhabdomyolysis, Reactive psychosis, Hyponatremic encephalopathy						
<b>General disorders and administration site conditions</b>						
DE006422	F/57	Chills	16Dec2010	Picolax	Recovered	Colonoscopy
<b>Investigations</b>						
AT006423	Unk/74	INR ratio increased	19-20Sept2010	Picolax	Unknown	Colonoscopy
AT006425	Unk/67	INR ratio increased	18-19Sept2011	Picolax	Unknown	Colonoscopy

## 8 Postmarket Experience

Sodium picosulfate, magnesium oxide and citric acid powder for oral solution is approved and marketed in countries outside the United States under the trade names of Picoprep, Picolax, PicoSalax, or Pico-Salax, varying by country. It is indicated for bowel cleansing prior to X-ray examination, endoscopy, or surgery. Approved in 1980 in the United Kingdom, PICOPREP, as of December 2010 had been approved and marketed in 10 countries. It is licensed in 23 countries.

In January 2012, based on an information request issued by DGIEP, the Applicant provided a search of the Ferring Global Safety database for cases of all forms of sodium picosulfate, i.e., PICOPREP, Picolax, Pico-salax (sodium picosulfate, magnesium oxide and citric acid), as well as Cilaxoral (sodium picosulfate). The search utilized the terms “gastrointestinal hemorrhage” that identified 6 cases and “ischemic colitis” that identified 16 total post marketing cases that included 4 of the cases identified in the gastrointestinal hemorrhage search. It should be noted that 5 of these cases were associated with use in patients with intestinal obstruction, a contraindication to PICOPREP use, and 1 case was associated with use for an off-label indication, i.e., treatment of severe impaction. Most of these reports have either limited additional information or the patients have other confounding factors that make attribution of the symptoms solely to the use of the drug difficult.

In March 2012, based on a consult to the Office of Safety and Epidemiology, Division of Pharmacovigilance 1 a report was generated to assist in response to a Citizen’s Petition concerns about ischemic colitis with PICOPREP use. Search of the Adverse Event Reporting System (AERS) database revealed one case of IC.

### **Case 6827323, ISR 6028710**

This case involved a 75-year-old male from Japan who received sodium picosulfate 10 mL in combination with Visiclear (sodium phosphate, monobasic, monohydrate, and sodium phosphate, dibasic anhydrous) 50 grams for colonoscopy bowel preparation (indication for colonoscopy was not reported). The sodium picosulfate was taken the day prior to the colonoscopy while Visiclear was taken the morning of the procedure. In addition, he also took 2 tablets of mosapride citrate, a prokinetic agent. Rectal bleeding started while the patient prepped with Visiclear. The colonoscopy revealed coagulated blood throughout the colon and ulcerations in the sigmoid colon.

A diagnosis of IC was made based upon the findings of the colonoscopy. The patient was treated with supportive care and recovered without any sequelae. His medical history is notable for previous myocardial infarction and hypertension. Concomitant medications included carvedilol, cilostazol, isosorbide mononitrate, azelnidipine and losartan potassium.<sup>22</sup>

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22 Cao,C, Consult Report Provision of Pharmacovigilance Data, March 29,2012, page 5.

**Reviewer Comment: The occurrence of this adverse event of IC appears to be multi-factorial. The patient was elderly with co-morbid cardiovascular disease. He also took sodium picosulfate with a sodium phosphate laxative. The contribution of the sodium picosulfate to IC is difficult to ascertain given pre-existing cardiac disease and concomitant laxative use.**

Post marketing monitoring is often difficult because many of the reports do not disclose full medical histories and concomitant drug usage which may be a factor in certain adverse events such as ischemic colitis.

A synopsis of relevant information from the Periodic Safety Update Reports is provided below .

### **Periodic Safety Update Reports**

**1) April 1, 2009-December 31, 2010-** There were 2 deaths reported . An 81-year-old female experienced cardiac arrest and ventricular tachycardia following treatment with Picolax, 2 dosage forms, for bowel preparation. ; A 73-year-old male developed fecal peritonitis, intestinal perforation, septicemic shock and renal failure following treatment with oral Picolax, 2 pouches, for preparation for barium enema.

No reports of hypermagnesemia were reported.

### **2) April 1,2008 – March 31, 2009**

There were 40 adverse event cases reported. A total of 13 case reports were serious and 14 case reports were classed as unexpected (serious or non-serious)

A total of 15 ADRs fulfilled criteria for inclusion as Line Listings in this time period. Gastrointestinal disorders and metabolism and nutrition disorders were the most frequently reported type of reaction.

There was one death reported; Case report 2009-00041FE An 82-year-old female, developed multi-organ failure, pseudo-obstruction, increased plasma magnesium, vomiting, nausea, and abdominal distension during treatment with oral Picolax, 1 pouch, for bowel cleansing prior to a colonoscopy.

### **3) April 1,2006- March 31,2008**

There were 75 adverse event case reports during this period; 35 case reports were serious. 34 case reports were classed as unexpected (serious or non-serious).

Gastrointestinal disorders, metabolic and nutrition disorders, and nervous system disorders were the most frequently reported events considered ADRs. Specific safety issues for this report period included hyponatremia, seizure, hypersensitivity and aphthoid ileal ulcer.

There were 4 deaths reported during this PSUR period; **Case Report 2006-01073FE**; a 14-year-old boy suffering from chronic constipation and severe fecal impaction was given Picolax for fecal impaction on 01 November 2006

**Case Report 2007-00124FE**; an 85-year-old man developed fecal peritonitis due to large intestinal obstruction with cecal perforation, following Picolax treatment as preparation for barium enema

**Case Report 2006-00398FE**; a 69-year-old man had taken PicoSalax (dose not reported) in preparation for a colonoscopy. He was also taking medication for diabetes (no further information reported). Collapsed after discharge post-colonoscopy

**Case Report 2007-00892FE**: this literature case report from Australia in 2006 was published as Leong DP, Kleinig TJ, Kimber TE, Bardy PG. Severe hypermagnesaemia related to laxative use in acute gastrointestinal graft-versus-host disease.

Specific safety issues included hyponatremia and other electrolyte imbalances. During the PSUR period 10 case reports of hyponatremia were received; 1 non-serious and 9 serious. 2 of the 10 cases of hyponatremia were associated with convulsions/epilepsy. 2 case reports of epileptic seizure/convulsion without hyponatremia were reported .

Five cases of aphthoid ileal ulcers were reported during this period. All occurred inpatients receiving PICOSALAX for bowel preparation prior to colonoscopy. All 5 cases were classed serious, unexpected and related

#### **4) April 1, 2001-March 31, 2006**

There were 50 adverse events case reports; 30 case reports were serious. The most common adverse drug reactions reported were those associated with the nervous system, followed by gastrointestinal then skin disorders. Specific safety issues included hyponatremia, epilepsy, and hypersensitivity

There were 2 deaths reported in this PSUR period. One patient died from respiratory failure after undergoing emergency surgery for perforation of a colon carcinoma.

One patient died due to multiple organ failure secondary to acute pancreatitis (gastrointestinal disorders) after receiving 1 dose of Picolax for an unreported indication. He developed acute pancreatitis the next day and subsequently suffered multi organ failure.

#### **5) October 18, 1995-March 31, 2001**

During the reporting period there were 48 suspected reactions to Picolax reported in 21 cases. The most frequently reported adverse drug reactions included vomiting, diarrhea, hyponatremia, and abdominal pain. The 5 cases of hyponatremia were

considered serious and expected in 4 cases but unexpected in 1 case.(hyponatremia due to over-hydration). The 5 serious cases of hyponatremia reported with concomitant events convulsion, hypokalemia, coma, and seizure. All case resolved without sequelae.

#### **6) June 1, 1990-October 17,1995**

There were 25 spontaneous reports for inclusion in the PSUR. No deaths were reported. Two safety issues were identified in the PSUR for this period: 1) allergic reactions i.e. urticaria and rash, also anaphylactoid reactions 2) excessive diarrhea and vomiting leading to hyponatremia and in isolated cases convulsions.

**Reviewer’s Comment: The safety profile of PICOPREP appears consistent with the known risks and adverse events reported for similar products in this drug class. More recent approvals such as Suprep , HalfLyte and Moviprep have labeled the most commonly occurring adverse events that may be experienced by patients using this class of drugs such as fluid shifts and electrolyte disturbances. Electrolyte abnormalities such as hyponatremia, hypokalemia, and hypocalcemia and dehydration are not novel occurrences in this drug class and product labels provide adequate warnings to better inform health professionals as to what populations should be considered for use when prescribing a bowel cleansing preparation. Fluid and electrolyte disturbances can lead to cardiac arrhythmias, seizures, and renal impairment.Secondary events such as seizures, syncope, or confusion may be related to dehydration and/or electrolyte abnormalities as well.**

**PICOPREP may modify the absorption of regularly prescribed medications and should be used with caution in certain patients such as those at increased risk for seizure.**

**While events such as exacerbation of inflammatory bowel disease and aphthoid ileal ulcers may be rare, they have been reported. There fore the potential for mucosal ulcerations resulting from the bowel preparation should be considered when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease.**

**Ischemic colitis is another rare adverse event that may be associated with the use of osmotic bowel preparations. There have been no reports of ischemic colitis in either study population for this NDA submission. The cases of ischemic colitis referenced above are reported from an international safety database.**

**Based on the safety data reported during the period covered by the PSURs, the overall benefit risk profile of PICOPREP appears favorable. Reported events were consistent with the known risk profile for osmotic bowel preparations.**

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**Unexpected adverse events occurred very rarely or were reported as isolated incidents and did not indicate any new safety signals.**

## 9 Appendices

### 9.1 Literature Review/References

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- 2 Eisen, Glen Importance of Split Dosing Bowel Preparation for Colonoscopy GI Digest Volume 1, June 2011.
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- 22 Cao,C, Consult Report Provision of Pharmacovigilance Data, March 29,2012, page 5.

## **9.2 Labeling Recommendations**

An additional bullet **5.8 Not for direct ingestion** should be included under the Warnings and Precautions section of the PICOPREP label. Discussions regarding labeling recommendations are ongoing at the time of this review.

## **9.3 Advisory Committee Meeting**

An advisory committee meeting was not convened regarding this application.

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/s/  
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ZANA H MARKS  
06/14/2012

ROBERT FIORENTINO  
06/19/2012

See separate CDTL memo for additional analyses and recommendations.