CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202535Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 13, 2012
From	Robert P. Fiorentino, M.D., M.P.H. Medical Team Leader CDER, Division of Gastroenterology & Inborn Errors
Subject	Cross-Discipline Team Leader Review
NDA# **Supplement#**	NDA 202535 Original
Applicant	Ferring Pharmaceuticals
Date of Submission	September 16, 2011
PDUFA Goal Date	July 16, 2012
Proprietary Name **Established (USAN) names**	Prepopik [submitted to NDA as PICOPREP] Sodium picosulfate, magnesium oxide, citric acid
Dosage forms / Strength	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
Proposed Indication(s)	Colon cleansing in preparation for colonoscopy
Recommended Action:	*Approval*

1. Introduction

On September 16, 2011, Ferring Pharmaceuticals submitted an original NDA for PICOPREP, a new molecular entity (NME) intended as an orally available bowel cleansing agent in preparation for colonoscopy. The results of two adequate and well controlled clinical trials were submitted under the NDA to support approval. The review was conducted under a Standard review timeline, with reviews submitted by multiple disciplines as described in Section 2.

Note that during the NDA review the proprietary product name of "PICOPREP" was determined to be unacceptable and resulted in a new name for the product, PREPOPIK. PICOPREP is used throughout this review to be consistent with other discipline reviews and with the applicant's original submission of datasets and tabulations presented in my review.

2. Background

General Background

Bowel Cleansing Products

See the Clinical Review by Dr. Zana Marks for information about the approval history of the various bowel preparation products and Section 11 of my CDTL review regarding the design of studies intended to support efficacy.

Compounds used for bowel cleansing can be divided into 3 broad categories according to their mechanism of action: *isosmotic, hyperosmotic* and *stimulant*.

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.

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.

Stimulant laxatives promote colonic motility through variable mechanisms that are incompletely characterized. Bisacodyl is a commonly used over the counter laxative and is used in combination with PEG-ELS solutions as a bowel cleansing agent, such as in HalfLytely. Its active metabolite stimulates colonic motility.

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.[1]

As discussed in detail in Dr. Marks' Clinical Review, the importance of a high-quality bowel preparation for the detection of colon polyps has been demonstrated in several studies.[2,3] 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 pathology. Furthermore, poor bowel preparation can prolong 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. Improvements in bowel preparation tolerability are important for increasing patient compliance with colorectal cancer screening guidelines, which in turn can lead to improved health outcomes.

As further addressed in Dr. Marks' review, split dosing (or 2-day 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.[3] One of the main concerns with respect to bowel preparations administered entirely the day before the procedure is the potential for

[1] Adamcewicz, M et al Mechanism of Action and Toxicities of Purgatrives Used for Colonoscopy Preparation, Expert Opin Drug Metab Toxicol.2011 January; 7(1): 89-101
[2] Leaper et al. Reasons for failure to diagnose colorectal carcinoma at colonoscopy. Endoscopy.204;36:499-503
[3] Harewood GC et al. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc.2003;58:76-79.

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 interval 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.[4]

Product

The product was submitted under the trade name, PICOPREP. The Division of Medication Error Prevention and Analysis (DMEPA) performed a review of the proposed proprietary name and concluded that the name is unacceptable. The applicant submitted a new name, **Prepopik**, which was later found to be acceptable by DMEPA. See Section 11 of my review for further discussion of this review issue.

Both PICOPREP and Prepopik are used interchangeably in my CDTL review to describe the product.

Prepopik (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. It 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. Magnesium citrate is a hyperosmotic agent.

Pre-submission Activity

PicoPrep was investigated under IND 101738.

A Type B, Pre-IND meeting was held on April 16, 2009 to obtain assistance from the Division regarding the development program for PICOPREP. Selected items of note from the 4/16/2009 meeting were the following:

- FDA noted that the sponsor would need to conduct the complete battery of reproductive toxicity studies with your product. For the marketing application, toxicology studies in a rodent and a nonrodent species for a minimum of 4 weeks duration with the combination you intend to market will be required
- Ferring proposed to conduct the required Segment II and Segment III reproductive toxicology studies in parallel with Phase 3 clinical studies. The FDA stated that Ferring can do that; however, adequate pregnancy precautions must be undertaken in the clinical trials.

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

- The FDA stated that a 15% NI margin is not recommended. Recent advice to sponsors for this indication has encouraged the use of a 9% margin [or smaller].
- FDA stated that for a product containing two or more drugs, evidence will be needed that each component makes a contribution to the claimed effects (21 CFR 300.50). FDA stated that the sponsor's development program will need to give consideration to how it will generate such evidence and noted that this would involve conducting studies using a factorial design, in which the combination is compared not only to placebo, but to each drug individually as well. Ferring stated that a factorial study would not be ethical because using only one component would not work. The FDA responded that a factorial design was not a requirement, but that some sort of evidence must be provided to support the need for the combination. If Ferring claims neither component alone would work, convincing evidence for that claim needs to be provided in the NDA.
- FDA stated that if there is substantial systemic exposure of sodium picosulfate, Ferring should conduct *in vitro* studies, including transporters and CYP 450 enzymes, to determine whether drug-drug interaction studies are needed. Since this product has not been approved before in the U.S., a thorough QTc study is strongly recommended if sodium picosulfate is bioavailable. FDA recommend Ferring submit the protocol for a Thorough QT study to the Agency for review and comment prior to initiating the QT study.

On January 05, 2011, the Sponsor received comments (Advice Letter) from the Agency for a protocol amendment and statistical analysis plan sent for review in April/May 2010. These comments were received after the clinical trial database had been locked. Selected items of note from the 1/05/2011 Advice Letter included the following comments:

- "Your proposed comparator, HalfLytely with 10 mg bisacodyl tablets, was approved based on a randomized, active-controlled, single-blind, multi-center, phase 3 study comparing HalfLytely with 10 mg bisacodyl tablets to HalfLytely with 20 mg bisacodyl tablets. The success rate of colonoscopy cleansing was 86.9% in the HalfLytely with 10 mg bisacodyl tablets group compared with 87.9% in the HalfLytely with 20 mg bisacodyl tablets group. This resulted in a difference of -1.0% in favor of HalfLytely with 20 mg bisacodyl tablets with a lower bound of 95% confidence interval of -7.2%. Therefore, the use of HalfLytely with 10 mg bisacodyl tablets as a control may contribute to loss of efficacy ("biocreep") as compared to the original HalfLytely product."
- "You propose a 9% non-inferiority margin. However, such a margin implies that a 10.6% relative decrease of the assumed event rate of 85% could result for patients treated with test drug as compared to patients treated with HalfLytely. This difference may not be acceptable from a clinical standpoint and will be a review issue. A more conservative approach would be to use a non-inferiority-margin of 4% so that a relative decrease in the event rate for the test drug is at most 5% for the demonstration of non-inferiority."

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.

- FDA noted that while the Phase 3 studies did not appear to show evidence of cardiac arrhythmias associated with the use of PicoPrep, these studies were neither powered nor designed to rule out a specific cardiac safety signal. In order to conclusively demonstrate that PicoPrep (unlike other drugs in this class) does not have the risk of rare, but serious arrhythmias associated with the use of other osmotic laxatives, an adequately designed clinical program would be required. The Sponsor clarified its understanding that class labeling, related to cardiac risk secondary to electrolyte imbalance, would be included in the labeling.
- 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 the submitted NDA application.

Submission and Review

Original NDA submitted on September 16, 2011. Satisfactory datasets were received. Application was granted a Standard Review. The assigned PDUFA goal date was July 16, 2012 and was not extended during the review. The submission was considered by the Pediatric Review Committee (PeRC) on 5/30/2011. The pediatric plan and Committee's recommendations are discussed in the Pediatrics section, below. No Advisory Committee meeting or CDER Regulatory Briefing was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon in my CDTL are the following:

DGIEP Clinical Review
- Zana Marks, M.D., M.P.H., review dated 6/19/2012

Office of Clinical Pharmacology, DCP III
- Dilara Jappar, Ph.D., review dated 5/22/2012

DGIEP Nonclinical Review
- Tamal K. Chakraborti, Ph.D., review dated 5/14/2012

ONDQA (CMC)
- Hitesh Shroff, Ph.D, reviews dated 5/16/2012 and 7/13/2012

Division of Biometrics 3 (Efficacy Statistics Review)
- Shahla Farr, review dated 6/19/2012

Division of Biometrics 3 (Safety Statistics Review)
- Bradley McEvoy, MS, DrPH, review dated 5/14/2012

Office of Safety and Epidemiology (OSE), Division of Pharmacovigilance-1 (DPV-1)
- Christian Cao, MPAS, PA-C, safety review dated 4/03/2012

Office of Scientific Investigations, Division of Good Clinical Practice Compliance
- Khairy W. Malek, M.D., Ph.D., review dated 6/20/2012

CDER DCRP QT Interdisciplinary Review Team
- Norman Stockbridge, M.D., Ph.D., Consult Review dated 3/20/2012

3. CMC

Facilities review/inspection

This NDA is recommended for approval from the ONDQA perspective. The chemistry reviewer concludes that the NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product.

The initial CMC review dated 5/16/2012 noted the following two issues:

1. The Office of Compliance has issued an overall "Withhold" recommendation.
2. Label/labeling issues were not resolved.

Because of these deficiencies, in the initial CMC Review, this NDA was not recommended for approval from the ONDQA perspective.

ONDQA submitted a second review dated 7/13/2012 concluding that these issues had been adequately resolved in the following manner:

> On July 9, 2012, the Office of Compliance issued the "Acceptable" recommendation for the facilities involved in the NDA.
>
> On July 13, 2012, the label and labeling were submitted and they are revised satisfactorily from the ONDQA perspective.

General product quality considerations

Picoprep contains three active ingredients: sodium picosulfate, anhydrous citric acid and magnesium oxide. Chemistry reviewed the relevant DMFs for each of these components and found them to be adequate.

Picoprep powder for oral administration is a white (b) (4) powder with a faint orange odor. Picoprep is packaged in a sachet (b) (4). Each sachet contains 16.1 g of powder. Picoprep contains the following inactive ingredients, potassium hydrogen carbonate, saccharin sodium (b) (4) and orange flavoring, (b) (4) spray dried (b) (4).

Table 1. Composition of PICOPREP sachets

Ingredients	Amount per dose	Function
Sodium picosulfate	10mg	Active ingredient
Magnesium oxide (b) (4)	3.5 g	Active ingredient
Anhydrous citric acid, anhydrous	12 g	Active ingredient
Potassium hydrogen carbonate (b) (4)	(b) (4)	
Saccharin sodium		
Orange flavoring, (b) (4) spray dried		

Source: Chemistry Review

ONDQA made the following conclusions in their review:

- The manufacturing process is satisfactorily reproducible and robust.
- The container closure system appears to be adequate (b) (4)
- All drug product batches comply with requirements for microbial tests.
- (b) (4) They are fully characterized in the drug substance DMF (b) (4) and controlled according to the drug product specification.
- The stability data provided are adequate and support the proposed 24-month expiration dating period for the drug product.
- The post-approval commitment for the stability studies is adequate.

In addition, CMC has provided a number of proposed revisions to the label that have been incorporated or are currently under labeling review.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review recommended the NDA for approval. Refer to the non-clinical review for a more detailed presentation of the nonclinical findings, which are summarized below.

The applicant has conducted several nonclinical studies with sodium picosulfate which include 14-day oral toxicology studies in rats and dogs and genotoxicity studies (Ames test, mouse lymphoma assay and *in vivo* mouse micronucleus test). In addition, the applicant also conducted toxicology studies with the drug product, which include 28-day oral toxicology studies in rats and dogs, and reproductive toxicology studies [i.e., fertility and early embryonic development to implantation study (Segment I) in rats, embryofetal development studies (Segment II) in rats and rabbits and pre and postnatal development study (Segment III) in rats].

The principal active component of PicoPrep, sodium picosulfate, was administered orally (gavage) for up to 14 days at doses (30, 300 and 1000 mg/kg BID) up to 1000 mg/kg BID

in rats and at doses (15, 150 and 600 mg/kg BID) up to 600 mg/kg BID in dogs (approximately 6000 and 3600 times the recommended human dose of 10 mg of sodium picosulfate in 16.13 g of drug product/pouch or 0.166 mg/kg of sodium picosulfate based on a 60 kg body weight), respectively. Treatment-related clinical signs included soft stools, diarrhea, and fecal staining, the expected pharmacological responses. Treatment-related clinical chemistry findings in rats include decrease in electrolytes (sodium, potassium and chloride) following administration of PicoPrep. In rats, sodium picosulfate caused increase in thickness of the intestine (elongated glandular crypts lined by immature, basophilic, epithelial cells) at all tested doses, minimal to mild mucosal hyperplasia of the small and large intestine (duodenum, jejunum, ileum, cecum, colon, and rectum) at all doses and mucosal hyperplasia associated with lymphocytic infiltration in the small intestine at ≥ 300 mg/kg BID doses (about 1800 times the recommended human dose of sodium picosulfate).

Sodium picosulfate was not mutagenic in the Ames test, mouse lymphoma assay and did not induce micronuclei in *in vivo* mouse bone marrow micronucleus test.

As per the nonclinical review, the applicant did not conduct reproductive toxicology studies with sodium picosulfate. However, the applicant provided literature references for the reproductive toxicology studies with sodium picosulfate. In oral fertility studies in rats, there was no significant treatment-related adverse effect of sodium picosulfate at dosage levels up to 100 mg/kg/day on mating performance and fertility. Sodium picosulfate was not teratogenic in rats up to 10,000 mg/kg/day and in rabbits up to 1000 mg/kg/day, PO. In a peri and postnatal development study in rats, animals were treated at 1, 10, and 100 mg/kg/day of sodium picosulfate. There were an increased number of dead pups at birth at 100 mg/kg/day. Postweaning growth, development, behavior and reproductive functions were unaffected by treatment with sodium picosulfate.

As described in the nonclinical review, PicoPrep was administered orally (gavage) for up to 28 days at doses (230, 750 and 2000 mg/kg BID) up to 2000 mg/kg BID in rats and at doses (230, 500 and 1000 mg/kg BID) up to 1000 mg/kg BID in dogs (about 8 and 4 times the recommended human dose, respectively). In a male and female oral fertility study (Segment I) in rats, PicoPrep did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area). Embryofetal development (Segment II) studies with PicoPrep have been performed in pregnant rats (230, 750 and 2000 mg/kg BID) and rabbits (230, 460 and 900 mg/kg BID) at doses up to 1.2 times and 1.1 times the recommended human dose, respectively, based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to PicoPrep. A pre and postnatal development (Segment III) study in rats, PicoPrep (230, 750 and 2000 mg/kg BID doses) showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area).

Absorption of sodium picosulfate has been investigated in rats following a single oral dose of 100mg/kg. Sodium picosulfate and its metabolites were not detected in either

serum or urine. The potential for the active diphenol metabolite (BHPM) of sodium picosulfate to enter the enterohepatic circulation was investigated in rats. There was very little biliary excretion in the first 6 hours after a single oral dose of 31umol/kg; however there was a significant biliary excretion between 6 and 18 hours postdose.

Sodium picosulfate was not reported to be excreted in breast milk (unknown if it is).

Overall, the nonclinical reviewer concluded that the safety of PicoPrep has been adequately tested in several toxicology studies. When the drug product was tested in rats and dogs, the no observed- adverse-effect-levels (NOAELs) were 2000 mg/kg BID (about 8 times the recommended clinical dose of 16.1 g BID or 533 mg/kg BID based on a 60-kg body weight) and 1000 mg/kg BID (about 4 times the recommended clinical dose of 16.1 g BID or 533 mg/kg BID based on a 60-kg body weight), respectively. Nonclinical reviewer concluded that the nonclinical studies conducted with PicoPrep provide adequate assurance of safety and support its proposed use at the intended therapeutic dosage and in accordance with the proposed product labeling.

In addition the non-clinical reviewer proposed the following revisions to the proposed labeling:

- Section 8.1 Pregnancy should be modified to reflect the dose based on the body surface area calculation. In addition, the findings of the pre and postnatal development study in rats need to be incorporated.
- Section 8.3 Nursing Mothers is in accordance with the regulations and states, "*It is not known whether this drug is excreted in human milk.*"
- Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility should be modified to state that genotoxicity studies were conducted with sodium picosulfate and not with the drug product, PicoPrep.
- (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

Refer to the Clinical Pharmacology review for a more detailed presentation of the pharmacology findings, which are summarized below.

General clinical pharmacology/biopharmaceutics considerations

The sponsor proposes that sodium picosulfate is metabolized by colonic bacteria (microorganism from the flora of large intestine) in colon to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM that acts directly on the colonic mucosa to stimulate colonic peristalsis. The small amount absorbed picosulfate is reported to be

excreted in the urine as a glucuronide-conjugate of BHPM. To support their statement regarding the metabolism by gut bacteria, the sponsor had submitted a single literature reference in which data is derived from "germ free" rats and rats who received antibiotics to purge their guts of bacteria (see clinical pharmacology review for details). The clinical pharmacology review noted that the applicant did not, however, provide human data to support their assertion that picosulfate is converted to BHPM in colon by colonic bacteria.

One phase 1 PK study was conducted to evaluate the PK parameters of picosulfate, Its active metabolite (BHPM) and magnesium in healthy volunteers following 1 dose (2 pouches separated by 6 hours) of PICOPREP. Following oral administration, both parent drug picosulfate and its active metabolite BHPM had very low systemic exposure. The mean (± SD) peak plasma concentration (Cmax) of picosulfate was 2.3 ± 1.4 ng/mL and 3.2 ± 2.6 ng/mL following the 1st and 2nd pouches separated by 6 hours, respectively, with Tmax of 1.9 ± 1.0 hours and 7.1 ± 2.1 hours (1.1 hours after the administration of 2nd dose) hours. The mean (± SD) amount of picosulfate recovered in urine was 0.019 ± 0.009 mg, representing approximately 0.19% of the administered dose.

The exposure of the active metabolite BHPM in plasma was lower compared to the parent drug picosulfate. Only 3 out of 16 subjects had quantifiable levels (above assay lower limit of quantification of 0.1 ng/mL) of BHPM in plasma. Due to this limited data, a thorough plasma PK analysis was not possible (the reported Cmax was 0.05 ng/mL). For the urine samples, 8 out of 16 subjects has measurable amount of free BHPM in urine, and the estimated percentage of free BHPM recovered in urine was 0.01%.

Drug-drug interactions

The sponsor evaluated potential drug-drug interaction of picosulfate by assessing its potential as an inhibitor or inducer of major drug-metabolizing cytochrome P450 enzymes. According to the clinical pharmacology review, human liver microsomes studies showed that picosulfate does not appear to be a direct, time-dependent or metabolism-dependent inhibitor of any of the CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) evaluated. Clinical Pharmacology reviewer concluded that there is no need of further *in vivo* DDI study.

The proposed label has a warning about co-administering a drug within one hour of the start of administration of PICOPREP.

Studies in cultured human hepatocytes showed that picosulfate does not appear to be an inducer of CYP1A2, CYP2B6 or CYP3A4/5 enzymes at concentrations up to 1.8 μM. According to the clinical pharmacology review, because PICOPREP is intended for one time use for colonoscopy, its induction potential is not considered critical.

The clinical pharmacology reviewer noted that PICOPREP may reduce the absorption of co-administered drug by decreasing the GI transit time due to its laxative affect. This potential drug interaction is addressed in the proposed label (as other bowel prep agents

have [redacted] (b) (4)

Thorough QT study or other QT assessment

The sponsor has requested a waiver of a thorough QT study in this submission. The QT/IRT team, after reviewing the waiver request, concluded that thorough QT assessment should be conducted to exclude effects on QT as PICOPREP has systemic bioavailability.

In the TQT Consult Memo to DGIEP, the reviewer states that, "PicoPrep has systemic bioavailability. Hence a thorough QT assessment should be conducted per the ICH-E14 Guidelines to exclude small effects on QT. The sponsor should submit a TQT study protocol for QT-IRT review prior to conduct the study."

I specifically note that the QT Interdisciplinary Review Team consult failed to mention anything about the known effects of PICOPREP on serum electrolytes and resultant effects on cardiac rhythm. In addition, they did not take into consideration the impracticalities of performing a TQT Study for bowel prep regimens, including how supratherapeutic exposures would be evaluated or whether this would even be needed.

The clinical pharmacology reviewer has similar concerns about the practicality of the study, especially when the systemic exposure at the therapeutic dose is low and a supratherapeutic dose may not be ethical to administer.

The results of ECG assessments with regarding to QT prolongation are discussed further in the Safety section of my CDTL memo (and presented in Table 30).

Given the very low absorption of picosulfate and its metabolites, the fact that the regimen is administered over a short term (at most split over two days), the likelihood that electrolyte shifts could confound the relationship between QT prolongation and pharmacokinetics, and the impracticality of giving supratherapeutic doses of picosulfate to healthy volunteers, I do not believe that a TQT study is warranted for the product.

Intrinsic / Extrinsic Factors

Pharmacokinetic of PICOPREP was not evaluated in renally or hepatically impaired patients. As per the clinical pharmacology review, the sponsor's rationale for not conducting these studies was that PICOPREP is intended for only "single-dose" administration. The ClinPharm reviewer notes that the phase 3 trials included, at screening, 379 patients with mild to moderate renal impairment, with creatinine clearance rates of <90 mL/min as determined by Cockcroft-Gault estimation, PK parameters of

PICOPREP cannot be compared between the renal impairment subjects and healthy subjects as picosulfate and BHPM were not measured in these phase 3 studies.

There is a potential for PICOPREP to cause electrolyte imbalances, however the current proposed label has warnings for its use in renally impaired patients, consistent with other colon cleansing agents.

Other notable issues

The clinical pharmacology review notes that in a single arm healthy volunteer study in 16 evaluable subjects, serum magnesium was evaluated for 48 hours after the administration of the first pouch. The raw maximum serum magnesium level was approximately 1.9 mEq/L, which is considered to be within the normal range (~1.5-2.5 mEq/L)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The sponsor conducted two phase 3 randomized, assessor blinded, multicenter studies to investigate the efficacy and safety of PICOPREP. Study FE2009-01 was a "split dose" study in which PICOPREP was administered the day before and the day of colonoscopy, whereas Study FE2009-02 was a "day before" study in which PICOPREP was administered the evening prior to the colonoscopy. In both studies, the active control arm was administered HalfLytely the day before colonoscopy (according to its approved dosing and administration). Both studies are discussed separately below. As noted by the statistical reviewer, placebo-controlled designs are neither practical nor ethical for these studies, as placebo subjects would potentially undergo a failed colonoscopy and need to repeat the procedure. In addition, the rationale for the design of the submitted studies is discussed in the context of factorial studies for combination products in Section 11 of my CDTL review.

In brief, the data from the two phase 3 studies indicate that the PicoPrep day-before regimen is non-inferior to the HalfLytely day-before regimen in colon cleansing in preparation for colonoscopy. Data from the split-dose study (FE2009-01) showed superiority of PicoPrep split dosing to day-before HalfLytely.

Refer to Dr. Zana Mark's clinical review for a more detailed overview of the clinical studies.

Table 2. Tabular Listing of Clinical Studies

Study ID	Study Design Overview	Objectives	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Treatment Duration
FE2009-01	Randomized, multicenter, assessor-blinded, parallel-group, active-control B/W "Split-Dose" PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy	To demonstrate non-inferiority of PicoPrep to HalfLytely in overall colon cleansing in preparation for colonoscopy; to determine the efficacy of ascending colon cleansing in a non-inferiority fashion; and to evaluate the safety, tolerability, and satisfaction of the preparation	**PicoPrep: split-dose**, 1 dose over 2 days; Each dose = 2 pouches: the night before (first pouch) and between 5 and 9 hours prior to colonoscopy (second pouch) **HalfLytely/ Bisacodyl Tablets Bowel Prep Kit:** 1-day dosing; the day prior to colonoscopy two 5 mg bisacodyl tablets and 2 L HalfLytely	**PicoPrep:** Dosed: 305 Completed: 304 **HalfLytely:** Dosed: 298 Completed: 295	**PicoPrep:** 1 dose as 2 pouches over 2 days **HalfLytely:** 1-day dosing
FE2009-02	Randomized, multicenter, assessor-blinded, parallel-group, active-control B/W "Day-Before" PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy	To demonstrate non-inferiority of PicoPrep to HalfLytely in overall colon cleansing in preparation for colonoscopy; to determine the efficacy of ascending colon cleansing in a non-inferiority fashion; and to evaluate the safety, tolerability, and satisfaction of the preparation	**PicoPrep: 1-day dosing**; Each dose = 2 pouches: the day prior to colonoscopy in the afternoon (first pouch) and approximately 6 hours later (second pouch) **HalfLytely/Bisacodyl Tablets Bowel Prep Kit:** 1-day dosing; the day prior to colonoscopy two 5 mg bisacodyl tablets and 2 L HalfLytely	**PicoPrep:** Dosed: 296 Completed: 287 **HalfLytely:** Dosed: 302 Completed: 295	**PicoPrep:** 1-day dosing **HalfLytely:** 1-day dosing

Source: Statistical Review (Shahla Farr), Table 1

Study FE2009-01: Two Day PICOPREP regimen vs. Day Before HalfLytely

The primary objective of Study FE2009-01 was to demonstrate non-inferiority of a PICOPREP 2-day regimen to the approved HalfLytely Day before regimen in overall colon cleansing in preparation for colonoscopy.

Subjects requiring an elective complete colonoscopy were screened for inclusion in the study. Those subjects who fulfilled all inclusion and no exclusion criteria were randomly assigned to either PICOPREP or HalfLytely. Patients were excluded from the study if the had acute surgical abdominal conditions, IBD, prior colorectal or upper GI surgery, colon disease or other GI disorder, uncontrolled angina/MI in last 3 months, CHF, uncontrolled HTN or renal insufficiency.

Subjects randomized to the PICOPREP treatment group were instructed to begin taking treatment (*first* reconstituted pouch) on the evening before colonoscopy and to complete taking treatment (second reconstituted pouch) the next day (the day of the colonoscopy) 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 HalfLytely 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 HalfLytely solution at a rate of one 8-ounce glass every 10 minutes. The HalfLytely treatment group completed treatment on the day before colonoscopy.

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. During the colonoscopy, the blinded assessor evaluated overall colon cleanliness using the Aronchick Scale (Table 33, Appendix 14) and cleanliness of the ascending colon, mid colon, and recto-sigmoid colon using the Ottawa Scale (Table 34 Appendix 14). Samples for laboratory determinations (hematology, coagulation, chemistry, and urinalysis) were collected at Visits 1, 3, 4, 5, and 6.

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 HalfLytely) was >-9% for the percentage of responders.

The key secondary variable was the proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent, Good, or Fair according to the Ottawa Scale at Visit 3 during colonoscopy.

Blinding

The subject and the site's designated unblinded coordinator knew the treatment group to which that subject was randomized; the designated unblinded coordinator instructed the subject in use of the bowel preparation and maintained the drug accountability binder that recorded study drug assignments. Both the unblinded coordinator and the subject signed a non-disclosure affidavit form designed to prevent both from disclosing which bowel preparation treatment the subject used. Treatment was blinded to the colonoscopist who assessed the efficacy of the 2 tested preparations and all of their assistants.

In case of a serious, unexpected or other important adverse event, an individual subject's treatment could be unblinded by opening a decoding envelope for that subject. The reason for any blind break, the date, and by whom the blind was broken were to be recorded in the CRF.

Statistical Considerations
Refer to the statistical review by Shahla Farr for a detailed description of the statistical considerations in this NDA.

The statistical reviewer of the IND had informed the sponsor that all randomized subjects should be used to define the primary analysis population; in a later communication, the sponsor agreed.

As noted in the statistical review of the NDA, the statistical reviewer of the IND had suggested a non-inferiority (NI) margin of 4%. Regardless, the sponsor still chose a 9% NI margin. 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% - 15%) was utilized, based on the Statistical Review and Evaluation of the HalfLytely 20 mg/2L Tablets. This estimates the M1 component of this study to be 70% (85% – 15%).

As described in the statistical review, the value of M2, the largest clinically acceptable difference of the test drug compared to the active control is typically computed by taking a fraction of M1. One common approach to determine M2 is to take one-half of the M1 interval, which, in this case, would be unacceptably high - 30% (0.5 x 70) because of high treatment effect and low placebo response. However, the NI margin (M2) of 9% was used for this study, based on clinical judgment and historical precedent with recently conducted phase 3 program that led to the approval of OsmoPrep, using a 10% NI margin (NDA 21-892). The historical data used by the sponsor is presented in more detail in the statistical review.

Results

A total of 608 subjects were randomized, 5 of which were not treated (2 PICOPREP, 3 HalfLytely). Of the 603 treated patients, 305 subjects received PICOPREP and 298 subjects received HalfLytely. Of these, 304 (99%) PICOPREP subjects and 295 (99%) HalfLytely subjects completed the study.

Analysis of Primary Endpoint

Based on Sponsor's results, 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. Therefore, the non-inferiority of PicoPrep to HalfLytely was demonstrated in both analysis sets. In addition, as prespecified in the statistical analysis plan, the lower bound of the CI was determined to be >0% and the superiority of PicoPrep were met.

Table 3. Non-inferiority Analysis for Percentage of Responders[a] Using the Aronchick Scale at Day of Colonoscopy [Visit 3] (ITT and PP Analysis Sets)

Analysis Set	PICOPREP	HalfLytely	Treatment Δ	1-Sided 97.5% CI
Intent-to-Treat	84% (256/304)	74% (221/297*)	10%	3.4[b]
Per Protocol	85% (235/277)	**76%** (207/274)	9%	2.7[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 and superior
Source: Sponsor's Table 9-1, CSR FE2009-01, page 49/80.

For the sponsor's ITT analysis, it should be noted that 2 HalfLytely subjects with unknown responder status were assigned as treatment failures (total n=297). In the statistical reviewer's analysis, these 2 patients did not appear in the dataset and were excluded (total n=295). Hence, the denominator in the statistical review for the ITT population is 297 whereas the applicant reports a denominator of 295. The 1-sided 97.5% CI of 3.4 is however the same in both analyses. The applicant and the statistical reviewer have concordant PP numbers.

The FDA Statistical reviewer also provided responder rates for each subscore of the Aronchick scale. Split-Dose PicoPrep had a numerically higher proportion of "Excellent" responders compared to Day-Before HalfLytely, as presented in Table 4.

Table 4. Percentages of Responders using the Aronchick Scale (ITT)

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

Source: FDA Statistical Review, Shahla Farr

This reviewer calculates the exact (binomial) confidence intervals around the point estimates for the "Excellent" rating in Table 4 to be PICOPREP 46% (40%, 51%) and HalfLytely 34% (29%, 40%).

The results of the same analysis in the Per Protocol population demonstrated similar results.

It should be noted that because Split Dose (2-day) bowel regimens are generally regarded as better than Day Before regimens (as discussed in Section 2), the comparison of Split Dose PicoPrep to Day-Before HalfLytely is somewhat of an unfair comparison with respect to establishing superiority. For superiority claims, it would be preferable to have split-dose vs. split-dose trial designs; however there is not a split-dose bisacodyl + HalfLytely regimen currently approved.

Analysis of Secondary Endpoints

As noted in the statistical review, the protocol-defined, 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 to be demonstrated if the 1-sided 97.5% CI for the treatment difference (PicoPrep minus HalfLytely) was >-9% for the percentage of responders.

Based on Sponsor's results, the percentage of responders for PicoPrep was greater than for HalfLytely for cleansing the ascending colon in both the ITT analysis set (89.5% versus 78.8%) and the PP analysis set (90.3% versus 79.2%). The non-inferiority of PicoPrep to HalfLytely 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.

(b) (4)

Regardless, as it can be gathered from Table 5, PicoPrep had a higher response rate than that of HalfLytely (90% vs. 79%). The lower bound of the 95% CI was above zero (5%).

Table 5. Statistical Reviewer's Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale

Ottawa Scale (Ascending Colon)	PicoPrep (n=303)	HalfLytely (n=295)	Difference 95% CI
Excellent + Good + Fair	272/303 (90%)	234/295 (79%)	10% (5%, 16%)
Fair + Poor	31/303 (10.2%)	61/295 (20.7%)	n/a

Source: Statistical Review
*Reviewer's analyses were based on dataset "ADFA" which was submitted by the Sponsor

Table 6 was taken from the Applicant's submission. It includes the response rates, the difference between the response rates along with the lower bound of the 1-sided 97.5% CI for both ITT and PP populations.

Table 6. Sponsor's Study Report - 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 (%)	HalfLytely n/N (%)	Treatment Difference: PICOPREP minus HalfLytely	1-Sided 97.5% CI
Intent-to-Treat Responders[a]	272/304 (89.5)	234/297 (78.8)	10.7	4.9[b]
Per Protocol Responders[a]	250/277 (90.3)	217/274 (79.2)	11.1	5.1[b]

Abbreviations: CI = confidence interval
PICOPREP Subject 103-019 and HalfLytely Subjects 104-038 and 105-021 with unknown responder status were classified as treatment failures.
a. Excellent, good, or fair rating.
Source: Statistical Review, Originally from Table 9-3 of Sponsor's Study Report, Page 51 of 80

Table 7 presents the response rates for the secondary endpoint variable for the ITT population.

Table 7. Study 2009-01 - Percentages of Responders using Secondary Endpoint (OTTAWA Score, Ascending Colon) (ITT)

Ottawa Scale (Ascending)	PicoPrep (n=303)	HalfLytely (n=295)
Excellent	**51 (17%)**	**21 (7%)**
Good	**76 (25%)**	**58 (20%)**
Fair	**145 (48%)**	**155 (53%)**
Poor	**29 (10%)**	**56 (19%)**
Inadequate	**2 (1%)**	**5 (2%)**

Source: Statistical Reviewers Analysis - Based on dataset "ADFA" submitted by the Sponsor (ITT)

(b) (4)

Other Endpoints

As noted in the Clinical Review, subject ratings of "tolerability and satisfaction" of the two preparations were rated by subjects. The preparation was apparently rated as easy or very easy to consume by 89.4% of PICOPREP subjects as compared to 29.1% of HalfLytely subjects. Also, the overall experience was rated as excellent by 46.8% of PICOPREP subjects as compared to 16.6% of HalfLytely subjects. Although the assessment of patient satisfaction lacks a validated scoring system, this data may provide insight into the potential for better adherence to the PICOPREP regimen compared to other PEG-ELS based regimens.

Subpopulations

Analysis of primary efficacy results by subpopulations of age, race and gender did not reveal clinically meaningful differences.

Study FE2009-02: Day Before Dosing of PICOPREP vs. Day Before HalfLytely

Study FE2009-002 was conducted similarly with respect to the study design and assessments as Study FE2009-01, with the primary difference being that PICOPREP was administered in a Day Before regimen. HalfLytely was also administered as a Day Before regimen (as in Study FE2009-01) according to its labeled Dosing and Administration.

In Study FE2009-002, those subjects who fulfilled all eligibility criteria were randomly assigned to 1 of the 2 preparations (PICOPREP or HalfLytely). At Visit 2, on the day before the colonoscopy, subjects were randomized to the PICOPREP treatment group were instructed to begin take the first reconstituted pouch evening before colonoscopy (Visit 3) and to take the second reconstituted pouch at least 6 hours later. 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 HalfLytely 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 HalfLytely solution at a rate of one 8-ounce glass every 10 minutes. The HalfLytely treatment therefore group completed treatment on the day before colonoscopy.

Results

In Study FE2009-002, 5 subjects were randomized manually, 2 to PICOPREP and 3 to HalfLytely. Five randomized subjects (4 PICOPREP, 1 HalfLytely) were not treated and were excluded from all analyses. A total of 598 subjects were enrolled and treated; 296 subjects were assigned to receive PICOPREP and 302 subjects were assigned to receive HalfLytely. Of these subjects, 287 of 296 (97.0%) PICOPREP subjects and 295 of 302 (97.7%) HalfLytely subjects completed the study. A total of 16 subjects discontinued the study.

Analysis of Primary Endpoint

Table 8 presents the results of the primary endpoint variable, the response rates as well as the difference in the two arms along with their associated 95% CI.

Table 8. 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 Difference: PICOPREP minus HalfLytely	1-Sided 97.5% CI
Intent-to-Treat	N	294	300		
	Responders[a], n (%)	244 (83.0)	239 (79.7)	3.3	-2.9[b]
Per Protocol	N	260	280		
	Responders[a], n (%)	216 (83.1)	222 (79.3)	3.8	-2.8[b]

Abbreviation: CI = confidence interval.
a. Excellent or good rating.
b. Non-inferior.
Source: Applicant FE2009-02 Clinical Study Report, Dated 11 July 2011

The results were similar in the two populations; in the PicoPrep arm for the ITT analysis set 49% and for PP analysis 48% of subjects had a response of "Excellent." However, in the HalfLytely group both the ITT and PP populations had 40% "Excellent" response. Table 9 presents the response rates for each individual element of the Aronchick Scale for the ITT and PP populations, respectively. This table was constructed by the statistical reviewer.

Table 9. Study 02 – Percentages of Responders using the Aronchick Scale (ITT)

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

Source: Statistical Review

For the ITT analysis, this reviewer calculates the exact 95%CI around the point estimates for PICOPREP as 49% (43%, 55%) and for HalfLytely as 40% (35%, 46%).

A similar analysis of the Per Protocol population yielded similar results.

Analysis of Secondary Endpoints

As noted in the statistical review, the protocol-defined, 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 to be demonstrated if the 1-sided 97.5% CI for the treatment difference (PicoPrep minus HalfLytely) was >-9% for the percentage of responders. (b) (4)

[redacted]

Table 10 shows the response rates for Ottawa Score (Ascending Colon), where subjects with response of "Excellent", "Good" and "Fair" have been combined in one category and subjects with responses of "Poor" and "Inadequate" combined in the second category.

Table 10. 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(%)	HalfLytely N(%)	Treatment Difference: PICOPREP- HalfLytely	1-Sided 97.5% CI
ITT Responders[a]	239/294 (81.3)	252/300 (84.0)	-2.7	-8.8[b]
PP Responders[a]	211/260 (81.2)	237/280 (84.6)	-3.5	-9.8

Abbreviations: CI = confidence interval, n=number of responders, N =number of subjects assessed, % = (n/N)*100 PICOPREP Subjects 202-042 and 204-044 with unknown responder status were classified as treatment failures.
a. Excellent, good, or fair rating.
b. Non-inferior.
Source: Statistical Review, original data from Table 9-3 of Sponsor's Study Report, Page 51 of 81

Based on Sponsor's results, the percentage of responders for HalfLytely was greater than PicoPrep for cleansing the ascending colon in both the ITT analysis set (81.3% versus 84%) and the PP analysis set (81.2% versus 84.6%). The non-inferiority of PicoPrep to HalfLytely in cleansing the ascending colon was indicated in ITT analysis set, only.

(b) (4)

[redacted]

Table 11 presents the response rates for the secondary endpoint variable for the ITT population according. The response rates for Ottawa Scale (ascending colon) by each score individually. PicoPrep has higher rates for scores of "Excellent" (15% vs. 10%).

Table 11. Percentages of Responders using Secondary Endpoint

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

Source: Statistical Review

Other Endpoints

As noted in the Clinical Review, subject ratings of "tolerability and satisfaction" the two preparations were rated by the subjects. Some of the clinically important treatment group differences were that the preparation was rated as easy or very easy to consume by 87.4%

of PICOPREP subjects and 37.2% of HalfLytely subjects. Also, the overall experience was rated as excellent by 45.5% of PICOPREP subjects and 19.1% of HalfLytely subjects.

The day before dosing results are similar to those reported for the split dose 2-day regimen. Again, although the assessment of patient satisfaction lacks a validated scoring system, this data may provide insight into the possibility of better adherence to the PICOPREP regimen compared to other PEG-ELS based regimens.

Subpopulations
Clinical Reviewer noted that an analysis of primary efficacy results by subpopulations of age, race and gender did not reveal clinically meaningful differences.

8. Safety

Both studies consisted of 6 visits, including Screening (Visit 1), day of randomization (Visit 2), day of colonoscopy (Visit 3), and 24-48 hours, 7 days, and 4 weeks 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.

Review of Adverse Events from Clinical Trials

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.

As noted in the clinical review, 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.

Table 12 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: ISS Table 3.2.1
Source: Clinical Review

Drug-related adverse events are described in the clinical review; however no specific additional safety concerns are evident from this data.

As noted by the clinical reviewer, the treatment-emergent adverse events and drug related treatment emergent adverse events listed do not constitute unexpected safety signals and are commonly associated with the use of bowel cleansing agents. 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 per labeled instructions and strict adherence to preparation and dosage instructions may decrease the occurrence of adverse events.

Split-Dose (2-Day) Study

Table 13 presents the summary of adverse events from the Split Dose Study, FE2009-01.

Table 13. Summary of Safety Results (Split-dose Dose)

	Study FE2009-01 (Split dose)	
	PICOPREP N=305 n (%)	HalfLytely N=298 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: Clinical Review, originally adapted from Table 10-1 (p 59/80) Section 10.1 CSR

Two (0.7%) subjects in the PICOPREP treatment group and 6 (2.0%) subjects in the HalfLytely treatment group reported TEAEs indicated as severe in intensity.

No subject died during the study. Serious adverse events were reported for 1 (0.3%) subject in the PICOPREP treatment group and 2 (0.7%) subjects in the HalfLytely treatment group. One (0.3%) subject in the HalfLytely treatment group experienced a TEAE that led to premature discontinuation of study drug.

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 HalfLytely treatment group, 6 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 (day of colonoscopy) 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.

The only ADRs reported by at least 1% of subjects in either treatment group were nausea, vomiting, headache, and chills and had similar occurrence in both arms.

The one serious adverse event in the PICOPREP arm (Subject 101-125) was a case of acute pancreatitis of unknown etiology assessed by the investigator as unrelated to study drug.

Two SAEs occurred in the HalfLytely arm, a report of colon cancer (Subject 102-036) and non-cardiac chest pain (Subject 107-019) on study Day 22.

One HalfLytely subject (106-092) had a TEAE of nausea that led to discontinuation of study drug.

Day Before Study

Table 14. Summary of Safety Results (Day-Before Dose)

	Study FE2009-02 (Day before dose)	
	PICOPREP N=305 n (%)	HalfLytely N=298 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)

Source: Clinical Review

The clinical reviewer has provided a detailed description of the narratives for the serious adverse events in her review.

Gastrointestinal disorders were reported for 61.8% of the PICOPREP group and 66.6% of the HalfLytely group. Neoplasms (benign, malignant and unspecified) were reported for 17.9% of the PICOPREP group and 20.2% of the HalfLytely group – reflecting the enrollment of subjects undergoing colorectal screening colonoscopies. The most commonly reported (≥10.0% of subjects) TEAEs in both treatment groups were resultant findings of the colonoscopy procedure, including hemorrhoids, diverticulum, colon adenoma, and colonic polyp.

In the PICOPREP treatment group, treatment-emergent adverse events designated by the investigator as severe in intensity included diverticulum and scar (colon scar tissue) (1 subject); colon cancer, anastomotic complication and dehydration (1 subject), acute coronary syndrome (1 subject), esophagitis (1 subject), and headache (1 subject).

Subject 212-072, a 49-year-old white female, developed ADRs of forceful 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 haemorrhage" was reported, which was considered unlikely to be related to study drug.

No subject died during the study. Serious adverse events were reported for 2 (0.7%) subjects in the PICOPREP treatment group and 1 (0.3%) subject in the HalfLytely treatment group. One (0.3%) subject in the HalfLytely treatment group experienced a TEAE that led to premature discontinuation of study drug.

Two (0.7%) PICOPREP subjects and 1 (0.3%) HalfLytely subject experienced serious TEAEs. One PICOPREP subject had colon cancer, anastomotic complications from surgery and dehydration. The other PICOPREP subject (212-043) was a 63 year old man who had acute coronary syndrome (with subsequent stent placement) on study Day 13 and noted as recovered on Day 16. CRF describes an ECG on Week 4 (Visit 6 follow-up) as having "new diffuse T wave inversion." Patient noted as "doing ok."

None of these SAEs was considered by the Investigator to be related to study drug and all had an outcome of recovered.

One (0.3%) subject in each treatment group experienced TEAEs that resulted in discontinuation from the study, both with vomiting.

Summary

In general I agree with the conclusion of the clinical reviewer that the adverse events in both studies were typical of the events experienced with the use of osmotic bowel cleansing preparations and were similar between the two regimens. Those that were atypical appear to be unrelated or secondary to other conditions.

It should be noted that more recent approvals such as Suprep, HalfLytely 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. I agree with the clinical reviewer's (Dr. Zana Marks) assertion that electrolyte abnormalities 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.

Evaluation of Laboratory Data

The Division of Biometrics VII (DB7) was consulted to provide a statistical safety review for Picoprep NDA #202535. The consult requested a targeted review focusing on potential safety issues associated with bowel preps, including changes in laboratory parameters related to the liver, electrolytes and kidney. The DB7 review's stated primary focus was to assess whether differences between the study treatments in laboratory parameters exist following administration of study drug, and whether the differences persist through the study follow-up. In addition, their consult review provides a detailed examination of the specific reported adverse events including: cardiac arrhythmia, seizure and ischemic colitis – at the request of the DGIEP clinical review team. Refer to the Division of Biometrics VII review dated 5/14/2012 for more details.

Both trials collected laboratory and adverse event information on the day of the colonoscopy and on three additional post-treatment follow-up visits over one month. Laboratory parameters were also assessed at baseline.

The protocol specified the following values to be collected and sent out to the central laboratory during Visit 1 and Visits 3-6:

- Hematology Panel: Full CBC and differential
- Coagulation Panel: PT, APTT
- Full chemistry panel: Calculated creatinine clearance, Serum magnesium (Mg++)
- Serum Chemistry: glucose, blood urea nitrogen (BUN), potassium, sodium, chloride, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT)
- Urinalysis Panel

Liver Enzymes

DB7 provided a review of alterations in liver enzymes over the course of schedule follow-up visits from baseline to 4 week follow-up (Visit 6).

Differences in the mean change from baseline lab values across the two treatment arms in Study 2009-01 are presented in Table 15 and the proportion of subjects with values outside normal range are presented in Table 16.

Table 15. Mean liver function values and difference in mean change from baseline (trial 2009-01)

Laboratory Parameter	Visit	PicoPrep mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Albumin (g/L)	BL	44.7 (44.4, 45.0)	44.7 (44.4, 44.9)	
	3	45.7 (45.4, 46.1)	45.3 (45.0, 45.6)	0.4 (-0.0, 0.8)
	4	43.8 (43.5, 44.1)	43.9 (43.6, 44.2)	-0.1 (-0.5, 0.2)
	5	43.9 (43.6, 44.2)	44.1 (43.8, 44.4)	-0.2 (-0.6, 0.1)
	6	44.1 (43.8, 44.4)	44.2 (43.9, 44.5)	-0.1 (-0.5, 0.3)
ALP (IU/L)	BL	72.8 (70.0, 75.7)	74.1 (70.0, 78.3)	
	3	74.2 (71.5, 76.8)	74.5 (70.6, 78.5)	1.2 (-0.2, 2.7)
	4	72.4 (69.4, 75.5)	73.0 (69.0, 77.0)	0.6 (-0.7, 1.9)
	5	71.6 (68.7, 74.6)	72.3 (68.6, 76.1)	0.1 (-1.3, 1.4)
	6	72.1 (68.9, 75.2)	72.8 (68.8, 76.7)	0.4 (-1.2, 2.0)
ALT (IU/L)	BL	26.0 (24.4, 27.7)	24.2 (22.7, 25.7)	
	3	28.0 (25.8, 30.2)	26.6 (23.5, 29.7)	-0.6 (-3.1, 1.9)
	4	26.3 (24.4, 28.2)	24.2 (21.6, 26.8)	0.2 (-1.8, 2.2)
	5	25.5 (23.6, 27.4)	24.0 (21.8, 26.2)	-0.3 (-2.2, 1.6)
	6	25.4 (23.5, 27.3)	23.3 (21.7, 24.9)	0.4 (-1.1, 1.8)
AST (IU/L)	BL	25.6 (24.4, 26.8)	24.7 (23.5, 25.9)	
	3	28.3 (26.3, 30.4)	27.6 (25.3, 29.9)	0.0 (-2.3, 2.3)
	4	25.4 (23.9, 26.8)	23.8 (22.4, 25.3)	0.6 (-0.7, 1.9)
	5	24.5 (23.3, 25.7)	23.5 (22.1, 24.9)	0.1 (-1.2, 1.4)
	6	25.1 (23.7, 26.5)	23.5 (22.2, 24.9)	0.7 (-0.5, 1.8)
Bilirubin (umol/L)	BL	7.8 (7.3, 8.3)	7.4 (7.0, 7.8)	
	3	13.3 (12.4, 14.1)	12.9 (12.1, 13.8)	-0.0 (-0.8, 0.8)
	4	7.4 (6.9, 7.9)	7.2 (6.7, 7.7)	-0.2 (-0.7, 0.3)
	5	7.3 (6.9, 7.8)	7.2 (6.7, 7.6)	-0.2 (-0.7, 0.2)
	6	7.8 (7.3, 8.3)	7.3 (6.8, 7.7)	0.1 (-0.3, 0.6)
GGT (IU/L)	BL	31.2 (27.1, 35.3)	30.0 (24.4, 35.5)	
	3	32.6 (27.8, 37.4)	29.8 (24.2, 35.4)	1.5 (-0.7, 3.8)
	4	30.3 (26.0, 34.7)	28.7 (23.0, 34.3)	0.5 (-1.0, 2.1)
	5	30.2 (26.1, 34.3)	28.8 (23.6, 34.0)	0.2 (-2.0, 2.4)
	6	31.7 (26.9, 36.6)	29.9 (24.3, 35.5)	0.6 (-2.4, 3.6)

DMC—Difference in mean change, BL=baseline assessment

Source: DB7 Safety Statistics review

Table 16. Liver function values outside normal range given normal at baseline (trial 2009-01)

Laboratory Parameter	Visit	PicoPrep n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Albumin	3	28/294 (9.5)	13/289 (4.5)	5.0 (0.9, 9.1)
	4	6/295 (2.0)	1/286 (0.3)	1.7 (-0.1, 3.4)
	5	5/296 (1.7)	4/286 (1.4)	0.3 (-1.7, 2.3)
	6	6/295 (2.0)	3/285 (1.1)	1.0 (-1.0, 3.0)
ALP	3	4/263 (1.5)	5/268 (1.9)	-0.3 (-2.5, 1.8)
	4	2/285 (0.7)	4/281 (1.4)	-0.7 (-2.4, 1.0)
	5	1/287 (0.3)	5/281 (1.8)	-1.4 (-3.1, 0.3)
	6	4/286 (1.4)	3/280 (1.1)	0.3 (-1.5, 2.1)
ALT	3	9/275 (3.3)	5/281 (1.8)	1.5 (-1.1, 4.1)
	4	9/278 (3.2)	2/279 (0.7)	2.5 (0.2, 4.8)
	5	9/279 (3.2)	5/280 (1.8)	1.4 (-1.1, 4.0)
	6	6/278 (2.2)	3/279 (1.1)	1.1 (-1.0, 3.2)
AST	3	15/255 (5.9)	9/265 (3.4)	2.5 (-1.1, 6.1)
	4	10/276 (3.6)	2/276 (0.7)	2.9 (0.5, 5.3)
	5	7/278 (2.5)	6/276 (2.2)	0.3 (-2.2, 2.9)
	6	6/277 (2.2)	5/275 (1.8)	0.3 (-2.0, 2.7)
Bilirubin	3	36/296 (12.2)	41/293 (14.0)	-1.8 (-7.3, 3.6)
	4	7/298 (2.3)	2/292 (0.7)	1.7 (-0.3, 3.6)
	5	4/299 (1.3)	0/292 (0.0)	1.3 (0.0, 2.6)
	6	4/298 (1.3)	0/291 (0.0)	1.3 (0.0, 2.6)
GGT	3	6/251 (2.4)	5/255 (2.0)	0.4 (-2.1, 3.0)
	4	6/252 (2.4)	1/252 (0.4)	2.0 (-0.1, 4.0)
	5	7/253 (2.8)	2/253 (0.8)	2.0 (-0.3, 4.3)
	6	6/252 (2.4)	8/252 (3.2)	-0.8 (-3.7, 2.1)

Source: DB7 Safety Statistics review

As noted by the DB7 statistics reviewer, at Visit 3 a statistically significantly greater percentage of patients that received PicoPrep had an albumin value outside the normal range (9.5% versus 4.5%; RD =5.0%; 95% CI= 0.9, 9.1). At visit 4 there are considerably fewer abnormal values, with the number being similar between treatment arms (PicoPrep 2.0% and HalfLytely 0.3%). The clinical significance of this observation is unclear, as the mean shift in the PicoPrep and HalfLytely groups are very similar (Table 15).

An similar analysis of liver function tests was performed for Study 2009-02, however other than shifts in albumin that were less pronounced that Study 2009-01, no clinically significant disturbances were noted. The results of these analyses are presented in Table 17 and Table 18.

Table 17. Mean liver function values and difference in mean change from baseline (trial 2009-02)

Laboratory Parameter	Visit	PicoPrep mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Albumin (g/L)	BL	45.0 (44.8, 45.3)	45.3 (45.0, 45.6)	-
	3	45.7 (45.4, 46.0)	45.1 (44.7, 45.4)	0.9 (0.5, 1.3)
	4	44.5 (44.2, 44.7)	44.3 (44.0, 44.6)	0.4 (0.1, 0.7)
	5	44.4 (44.1, 44.7)	44.5 (44.2, 44.7)	0.2 (-0.1, 0.6)
	6	44.4 (44.1, 44.7)	44.4 (44.2, 44.7)	0.2 (-0.1, 0.6)
ALP (IU/L)	BL	71.3 (69.1, 73.5)	71.3 (69.1, 73.5)	-
	3	72.1 (69.9, 74.3)	71.2 (68.9, 73.5)	0.8 (-0.5, 2.0)
	4	70.1 (68.1, 72.1)	70.6 (68.5, 72.8)	0.2 (-1.1, 1.4)
	5	70.1 (67.8, 72.4)	70.9 (68.8, 73.0)	-0.7 (-2.2, 0.8)
	6	70.7 (68.4, 73.0)	70.9 (68.7, 73.0)	-0.2 (-1.8, 1.3)
ALT (IU/L)	BL	25.0 (22.9, 27.1)	25.6 (23.7, 27.6)	-
	3	26.2 (24.5, 27.9)	26.8 (24.7, 28.8)	-0.1 (-1.9, 1.8)
	4	25.1 (23.6, 26.7)	26.0 (24.0, 28.1)	-0.3 (-2.4, 1.8)
	5	23.4 (21.6, 25.2)	24.9 (23.0, 26.7)	-1.0 (-3.1, 1.1)
	6	24.6 (23.1, 26.0)	26.0 (24.0, 28.0)	-1.0 (-3.2, 1.2)
AST (IU/L)	BL	23.4 (22.4, 24.4)	25.0 (23.6, 26.3)	-
	3	26.2 (24.9, 27.6)	27.2 (25.5, 28.9)	0.6 (-0.7, 1.9)
	4	24.0 (22.9, 25.2)	25.2 (23.7, 26.7)	0.4 (-0.9, 1.8)
	5	22.5 (21.5, 23.6)	24.5 (23.0, 26.0)	-0.4 (-1.8, 1.0)
	6	23.3 (22.3, 24.2)	24.6 (23.1, 26.0)	0.2 (-0.9, 1.4)
Bilirubin (umol/L)	BL	7.8 (7.3, 8.3)	7.7 (7.2, 8.1)	-
	3	12.7 (11.9, 13.4)	12.6 (11.9, 13.3)	0.0 (-0.6, 0.6)
	4	7.5 (7.0, 7.9)	7.2 (6.8, 7.7)	0.2 (-0.2, 0.6)
	5	7.3 (6.8, 7.8)	7.2 (6.8, 7.7)	-0.1 (-0.5, 0.4)
	6	7.6 (7.1, 8.1)	7.5 (7.0, 8.0)	0.0 (-0.4, 0.5)
GGT (IU/L)	BL	30.7 (26.7, 34.8)	33.5 (28.0, 39.1)	-
	3	29.9 (26.1, 33.6)	34.1 (28.2, 40.0)	-0.8 (-3.0, 1.3)
	4	28.8 (25.5, 32.0)	33.0 (27.2, 38.8)	-1.3 (-3.8, 1.2)
	5	29.1 (25.7, 32.5)	32.3 (27.0, 37.7)	-1.3 (-4.2, 1.7)
	6	32.1 (27.7, 36.6)	33.6 (27.8, 39.4)	0.7 (-2.3, 3.7)

DMC—difference in mean change, BL=baseline assessment

Source: DB7 Safety Statistics review

Table 18. Liver function values outside normal range given normal at baseline (trial 2009-02)

Laboratory Parameter	Visit	PicoPrep n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Albumin	3	16/277 (5.8)	8/283 (2.8)	2.9 (-0.4, 6.3)
	4	2/275 (0.7)	3/279 (1.1)	-0.3 (-1.9, 1.2)
	5	2/275 (0.7)	7/279 (2.5)	-1.8 (-3.9, 0.3)
	6	1/275 (0.4)	3/284 (1.1)	-0.7 (-2.1, 0.7)
ALP	3	2/276 (0.7)	3/276 (1.1)	-0.4 (-1.9, 1.2)
	4	2/278 (0.7)	2/283 (0.7)	0.0 (-1.4, 1.4)
	5	3/277 (1.1)	4/283 (1.4)	-0.3 (-2.2, 1.5)
	6	1/275 (0.4)	2/289 (0.7)	-0.3 (-1.5, 0.9)
ALT	3	10/271 (3.7)	9/277 (3.2)	0.4 (-2.6, 3.5)
	4	10/269 (3.7)	7/275 (2.5)	1.2 (-1.8, 4.1)
	5	3/269 (1.1)	10/276 (3.6)	-2.5 (-5.0, 0.0)
	6	5/269 (1.9)	12/280 (4.3)	-2.4 (-5.3, 0.4)
AST	3	19/272 (7.0)	10/265 (3.8)	3.2 (-0.6, 7.0)
	4	8/273 (2.9)	11/271 (4.1)	-1.1 (-4.2, 2.0)
	5	2/273 (0.7)	4/271 (1.5)	-0.7 (-2.5, 1.0)
	6	5/271 (1.8)	10/277 (3.6)	-1.8 (-4.5, 1.0)
Bilirubin	3	24/281 (8.5)	23/289 (8.0)	0.6 (-3.9, 5.1)
	4	2/280 (0.7)	1/287 (0.3)	0.4 (-0.8, 1.6)
	5	1/279 (0.4)	0/288 (0.0)	0.4 (-0.3, 1.1)
	6	3/279 (1.1)	3/292 (1.0)	0.0 (-1.6, 1.7)
GGT	3	11/245 (4.5)	4/244 (1.6)	2.9 (-0.2, 5.9)
	4	10/242 (4.1)	3/239 (1.3)	2.9 (-0.0, 5.8)
	5	7/241 (2.9)	4/240 (1.7)	1.2 (-1.4, 3.9)
	6	12/241 (5.0)	9/244 (3.7)	1.3 (-2.3, 4.9)

Source: DB7 Statistics Review

Electrolyte Values and Renal Function Tests

Refer to the DB7 statistical review for a very detailed analysis of electrolyte and renal function tests during the study.

Mean Shift Analysis

Mean laboratory value and difference in mean change from baseline of selected laboratory parameters are for both studies in Table 19 (Study 2009-01) and

Table 20 (Study 2009-02). Notable is that PICOPREP is associated with an increase in serum magnesium (due to the magnesium oxide component). However the overall *mean* changes from baseline for all parameters presented are clinically insignificant.

For instance, in the split dose study, 23% of patients with a normal value at baseline in the PICOPREP arm had ≥ 1 abnormal electrolyte value on the day of colonoscopy. While

patients experienced slight changes in electrolytes such as sodium, potassium, chloride, magnesium and urea, these changes had returned to normal by the next follow-up visit scheduled 24-48 hours after the colonoscopy and generally were not found to be of clinical significance. These findings were similar in both the split-dose and the day-before dose studies.

Table 19. Mean laboratory value and difference in mean change from baseline (trial 2009-01)

Laboratory Parameter	Visit	PicoPrep Mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Potassium (mmol/L)	BL	4.21 (4.17, 4.26)	4.26 (4.21, 4.31)	
	3	4.11 (4.05, 4.16)	4.18 (4.12, 4.23)	-0.03 (-0.10, 0.04)
	4	4.15 (4.10, 4.20)	4.12 (4.08, 4.17)	0.07 (0.01, 0.14)
	5	4.18 (4.13, 4.23)	4.24 (4.18, 4.29)	-0.01 (-0.08, 0.06)
	6	4.15 (4.11, 4.20)	4.23 (4.18, 4.27)	-0.03 (-0.09, 0.04)
Sodium (mmol/L)	BL	139.6 (139.4, 139.9)	139.7 (139.5, 140.0)	
	3	138.9 (138.6, 139.2)	139.6 (139.3, 139.9)	-0.6 (-0.9, -0.2)
	4	139.3 (139.0, 139.5)	139.4 (139.2, 139.7)	-0.0 (-0.4, 0.3)
	5	139.5 (139.3, 139.8)	139.5 (139.2, 139.7)	0.2 (-0.1, 0.5)
	6	139.5 (139.2, 139.7)	139.5 (139.2, 139.8)	0.1 (-0.3, 0.4)
Chloride (mmol/L)	BL	102.7 (102.4, 102.9)	102.7 (102.4, 103.0)	
	3	100.9 (100.5, 101.2)	102.5 (102.2, 102.8)	-1.6 (-2.0, -1.2)
	4	102.6 (102.3, 102.9)	103.0 (102.7, 103.3)	-0.3 (-0.7, 0.0)
	5	102.9 (102.6, 103.2)	102.7 (102.4, 103.0)	0.3 (-0.1, 0.6)
	6	102.8 (102.5, 103.1)	102.8 (102.5, 103.1)	0.0 (-0.3, 0.4)
Magnesium (mmol/L)	BL	0.86 (0.85, 0.87)	0.86 (0.85, 0.87)	
	3	0.98 (0.97, 0.99)	0.86 (0.85, 0.87)	0.12 (0.11, 0.14)
	4	0.85 (0.84, 0.86)	0.83 (0.82, 0.84)	0.02 (0.01, 0.03)
	5	0.83 (0.83, 0.84)	0.85 (0.84, 0.86)	-0.02 (-0.03, -0.01)
	6	0.84 (0.83, 0.85)	0.85 (0.84, 0.86)	-0.01 (-0.02, 0.00)
Calcium (mmol/L)	BL	2.37 (2.36, 2.38)	2.36 (2.35, 2.37)	
	3	2.37 (2.35, 2.38)	2.37 (2.36, 2.38)	-0.01 (-0.03, 0.00)
	4	2.33 (2.32, 2.35)	2.33 (2.32, 2.34)	-0.01 (-0.02, 0.01)
	5	2.35 (2.34, 2.36)	2.34 (2.33, 2.35)	0.00 (-0.01, 0.02)
	6	2.35 (2.34, 2.37)	2.36 (2.35, 2.37)	-0.01 (-0.03, 0.00)
Creatinine (umol/L)	BL	74.0 (72.0, 76.0)	74.0 (72.3, 75.7)	
	3	74.9 (73.0, 76.9)	75.4 (73.8, 77.0)	-0.9 (-2.1, 0.3)
	4	77.4 (75.2, 79.7)	75.9 (74.2, 77.6)	1.4 (0.1, 2.8)
	5	76.1 (74.0, 78.2)	76.0 (74.3, 77.7)	-0.2 (-1.5, 1.1)
	6	76.5 (74.5, 78.5)	76.1 (74.4, 77.8)	0.4 (-1.0, 1.8)
EGFR	BL	114.6 (110.4, 118.9)	112.9 (108.6, 117.3)	
	3	111.2 (107.3, 115.1)	109.0 (104.8, 113.2)	0.3 (-2.1, 2.7)
	4	108.7 (104.7, 112.7)	108.7 (104.6, 112.7)	-1.5 (-4.0, 1.0)
	5	111.1 (107.1, 115.2)	109.2 (105.1, 113.3)	0.6 (-1.9, 3.0)
	6	110.0 (106.0, 114.0)	108.2 (104.2, 112.2)	-0.3 (-2.8, 2.3)
Urea (mmol/L)	BL	5.5 (5.3, 5.7)	5.6 (5.4, 5.8)	
	3	4.1 (3.9, 4.2)	4.3 (4.2, 4.5)	-0.2 (-0.4, 0.0)
	4	5.3 (5.1, 5.5)	5.2 (5.1, 5.4)	0.1 (-0.1, 0.3)
	5	5.4 (5.3, 5.6)	5.5 (5.3, 5.7)	0.0 (-0.2, 0.2)
	6	5.6 (5.4, 5.8)	5.6 (5.4, 5.8)	0.0 (-0.2, 0.2)

DMC—Difference in mean change, BL=baseline assessment

Source: DB7 Statistical Review

Table 20. Mean laboratory value and difference in mean change from baseline (trial 2009-02)

Laboratory Paramter	Visit	PicoPrep mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Potassium (mmol/L)	BL	4.19 (4.15, 4.24)	4.19 (4.15, 4.24)	
	3	4.21 (4.16, 4.26)	4.13 (4.08, 4.17)	0.08 (0.01, 0.15)
	4	4.12 (4.07, 4.16)	4.09 (4.04, 4.13)	0.03 (-0.03, 0.09)
	5	4.18 (4.14, 4.22)	4.15 (4.10, 4.20)	0.02 (-0.05, 0.08)
	6	4.16 (4.12, 4.21)	4.14 (4.09, 4.18)	0.02 (-0.05, 0.08)
Sodium (mmol/L)	BL	139.4 (139.2, 139.6)	139.3 (139.1, 139.6)	
	3	139.6 (139.4, 139.9)	139.8 (139.6, 140.1)	-0.3 (-0.6, 0.1)
	4	139.3 (139.1, 139.5)	139.6 (139.3, 139.8)	-0.3 (-0.6, -0.0)
	5	139.5 (139.2, 139.7)	139.3 (139.1, 139.6)	0.0 (-0.3, 0.4)
	6	139.4 (139.1, 139.6)	139.3 (139.1, 139.6)	-0.0 (-0.4, 0.3)
Chloride (mmol/L)	BL	102.6 (102.4, 102.9)	102.4 (102.2, 102.7)	
	3	101.7 (101.3, 102.0)	102.7 (102.4, 103.0)	-1.2 (-1.6, -0.8)
	4	102.4 (102.1, 102.7)	103.0 (102.7, 103.2)	-0.7 (-1.1, -0.4)
	5	102.5 (102.2, 102.8)	102.4 (102.1, 102.7)	-0.1 (-0.5, 0.2)
	6	102.4 (102.1, 102.7)	102.5 (102.2, 102.8)	-0.4 (-0.7, 0.0)
Magnesium (mmol/L)	BL	0.86 (0.86, 0.87)	0.86 (0.85, 0.87)	
	3	0.98 (0.97, 0.99)	0.85 (0.84, 0.86)	0.13 (0.11, 0.14)
	4	0.85 (0.84, 0.86)	0.83 (0.83, 0.84)	0.01 (0.00, 0.03)
	5	0.85 (0.84, 0.85)	0.84 (0.83, 0.85)	0.00 (-0.01, 0.02)
	6	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.00 (-0.01, 0.01)
Calcium (mmol/L)	BL	2.38 (2.37, 2.39)	2.39 (2.38, 2.40)	
	3	2.39 (2.38, 2.40)	2.37 (2.36, 2.38)	0.02 (0.01, 0.04)
	4	2.37 (2.35, 2.38)	2.36 (2.35, 2.37)	0.01 (-0.00, 0.03)
	5	2.37 (2.36, 2.38)	2.36 (2.35, 2.37)	0.01 (-0.00, 0.03)
	6	2.36 (2.35, 2.38)	2.35 (2.34, 2.36)	0.02 (0.00, 0.03)
Creatinine (umol/L)	BL	73.5 (71.7, 75.4)	72.8 (71.0, 74.6)	
	3	76.1 (74.2, 78.0)	75.0 (73.1, 77.0)	0.3 (-1.1, 1.8)
	4	77.2 (75.1, 79.3)	74.7 (72.7, 76.7)	1.6 (0.0, 3.2)
	5	74.9 (73.0, 76.8)	73.6 (71.8, 75.4)	0.4 (-0.9, 1.6)
	6	75.5 (73.6, 77.5)	74.2 (72.4, 76.0)	0.3 (-1.1, 1.8)
EGFR	BL	108.3 (104.7, 111.9)	111.8 (108.0, 115.6)	
	3	103.5 (100.0, 107.0)	108.0 (104.0, 111.9)	-1.1 (-3.2, 1.1)
	4	103.2 (99.7, 106.7)	108.6 (104.7, 112.6)	-2.4 (-4.5, -0.2)
	5	106.0 (102.5, 109.5)	109.7 (105.8, 113.6)	-0.5 (-2.5, 1.4)
	6	105.8 (102.2, 109.5)	108.9 (105.1, 112.8)	-0.1 (-2.2, 2.1)
Urea (mmol/L)	BL	5.5 (5.3, 5.7)	5.7 (5.5, 5.9)	
	3	4.1 (4.0, 4.3)	4.5 (4.3, 4.6)	-0.2 (-0.4, 0.1)
	4	5.2 (5.0, 5.3)	5.2 (5.1, 5.4)	0.1 (-0.1, 0.3)
	5	5.6 (5.4, 5.8)	5.6 (5.4, 5.8)	0.1 (-0.1, 0.3)
	6	5.5 (5.4, 5.7)	5.7 (5.5, 5.8)	0.0 (-0.2, 0.3)

DMC—Difference in mean change, BL – baseline assessment

Source: DB7 Statistical Review

Outside Normal Range Analysis

Data was also similarly analyzed to evaluate the frequency of electrolyte abnormalities that fell outside of normal ranges.

Table 21 presents the reference ranges for laboratory parameters used to define the limits of normal ranges.

Table 21. Reference ranges for laboratory parameters

Laboratory Parameter (abbreviation, units)	Lower Limit	Upper Limit
Albumin (ALB, g/L)	37	49
Alkaline Phosphatase (ALP, IU/L)	40	135
Alanine Transaminase (ALT, IU/L)	0	47
Aspirate Transaminase (AST, IU/L)	0	37
Calcium (CA, mmol/L)	2.1	2.55
Bilirubin (CBILI, umol/L)	0	19
Chloride (CL, mmol/L)	95	113
Creatine Clearance (EGFR,)	90	
Creatinine (CREATENZ, umol/L)	45 (F); 59 (M)	84 (F); 104 (M)
Gamma Glutamly Transpeptiase (GGT, IU/L)	0	33 (F); 51 (M)
Potassium (K, mmol/L)	3.6	5.2
Magnesium (MG, mmol/L)	0.7	1.05
Sodium (SODIUM, mmol/L)	134	146
Urea (UREA, mmol/L)	3.2	8.6

F—females; M—males.

Source: DB7 Statistics review

In the Split Dose Study (2-day regimen of PICOPREP), subjects in the PICOPREP arm on the day of colonoscopy appeared to have more frequent shifts below the normal range for potassium (7.3% vs. 4.1%), sodium (3.7% vs. 1.0%) and chloride (3.7% vs. 0.3%). Most notable is an 11.6% shift in magnesium above the normal range in the PICOPREP arm on the day of colonoscopy, with no subjects having such a shift in the HalfLytely arm. As noted by the DB7 statistics reviewer, compared to HalfLytely, patients that received PicoPrep had a significantly greater increase in the mean change in serum magnesium from baseline at visit 3 (Δ=0.12 mmol/L; 95% CI=0.11, 0.14). However this imbalance quickly resolved by Visit 4 (24 to 48 hours later), with no apparent differences between the two arms thereafter.

Table 22. Number of patients above or below normal range (trial 2009-01)

Laboratory Parameter	Visit	Below		Above	
		PicoPrep n/N (%)	HalfLytely n/N (%)	PicoPrep n/N (%)	HalfLytely n/N (%)
Potassium	3	19/260 (7.3)	11/268 (4.1)	7/260 (2.7)	5/268 (1.9)
	4	15/282 (5.3)	10/279 (3.6)	4/282 (1.4)	1/279 (0.4)
	5	11/285 (3.9)	8/279 (2.9)	5/285 (1.8)	8/279 (2.9)
	6	11/284 (3.9)	8/278 (2.9)	2/284 (0.7)	2/278 (0.7)
Sodium	3	11/298 (3.7)	3/295 (1.0)	0/298 (0.0)	2/295 (0.7)
	4	4/299 (1.3)	5/292 (1.7)	0/299 (0.0)	0/292 (0.0)
	5	2/300 (0.7)	1/292 (0.3)	1/300 (0.3)	1/292 (0.3)
	6	2/299 (0.7)	3/291 (1.0)	1/299 (0.3)	2/291 (0.7)
Chloride	3	11/301 (3.7)	1/298 (0.3)	0/301 (0.0)	0/298 (0.0)
	4	2/302 (0.7)	2/295 (0.7)	0/302 (0.0)	0/295 (0.0)
	5	1/303 (0.3)	3/295 (1.0)	0/303 (0.0)	0/295 (0.0)
	6	2/302 (0.7)	3/294 (1.0)	0/302 (0.0)	0/294 (0.0)
Magnesium	3	0/294 (0.0)	0/294 (0.0)	34/294 (11.6)	0/294 (0.0)
	4	2/296 (0.7)	2/291 (0.7)	0/296 (0.0)	0/291 (0.0)
	5	4/297 (1.3)	0/291 (0.0)	0/297 (0.0)	1/291 (0.3)
	6	7/296 (2.4)	1/290 (0.3)	1/296 (0.3)	2/290 (0.7)
Calcium	3	2/292 (0.7)	1/286 (0.3)	4/292 (1.4)	6/286 (2.1)
	4	0/292 (0.0)	1/283 (0.4)	2/292 (0.7)	5/283 (1.8)
	5	0/293 (0.0)	1/283 (0.4)	5/293 (1.7)	3/283 (1.1)
	6	0/292 (0.0)	1/282 (0.4)	7/292 (2.4)	4/282 (1.4)
Creatinine	3	2/260 (0.8)	2/268 (0.7)	5/260 (1.9)	13/268 (4.9)
	4	2/264 (0.8)	1/267 (0.4)	18/264 (6.8)	11/267 (4.1)
	5	1/264 (0.4)	0/267 (0.0)	10/264 (3.8)	13/267 (4.9)
	6	1/264 (0.4)	1/265 (0.4)	11/264 (4.2)	14/265 (5.3)
eGFR	3	22/221 (10.0)	17/214 (7.9)	0/221 (0.0)	0/214 (0.0)
	4	32/223 (14.3)	22/212 (10.4)	0/223 (0.0)	0/212 (0.0)
	5	22/223 (9.9)	17/213 (8.0)	0/223 (0.0)	0/213 (0.0)
	6	24/223 (10.8)	21/211 (10.0)	0/223 (0.0)	0/211 (0.0)
Urea	3	60/287 (20.9)	33/276 (12.0)	0/287 (0.0)	0/276 (0.0)
	4	12/287 (4.2)	6/274 (2.2)	4/287 (1.4)	3/274 (1.1)
	5	13/288 (4.5)	4/274 (1.5)	4/288 (1.4)	7/274 (2.6)
	6	8/287 (2.8)	5/272 (1.8)	9/287 (3.1)	7/272 (2.6)

Source: DB7 Statistics review

Table 23. Number of patients above or below normal range (trial 2009-02)

Laboratory Parameter	Visit	Below		Above	
		PicoPrep n/N (%)	HalfLytely n/N (%)	PicoPrep n/N (%)	HalfLytely n/N (%)
Potassium	3	13/274 (4.7)	13/271 (4.8)	0/274 (0.0)	1/271 (0.4)
	4	8/276 (2.9)	9/277 (3.2)	1/276 (0.4)	0/277 (0.0)
	5	6/276 (2.2)	14/278 (5.0)	2/276 (0.7)	0/278 (0.0)
	6	7/275 (2.5)	8/284 (2.8)	1/275 (0.4)	3/284 (1.1)
Sodium	3	3/286 (1.0)	3/295 (1.0)	0/286 (0.0)	0/295 (0.0)
	4	4/284 (1.4)	1/291 (0.3)	0/284 (0.0)	0/291 (0.0)
	5	1/285 (0.4)	1/291 (0.3)	0/285 (0.0)	0/291 (0.0)
	6	1/284 (0.4)	1/296 (0.3)	0/284 (0.0)	0/296 (0.0)
Chloride	3	3/287 (1.0)	0/297 (0.0)	0/287 (0.0)	0/297 (0.0)
	4	1/285 (0.4)	0/293 (0.0)	0/285 (0.0)	0/293 (0.0)
	5	0/285 (0.0)	0/293 (0.0)	0/285 (0.0)	0/293 (0.0)
	6	0/285 (0.0)	0/298 (0.0)	0/285 (0.0)	0/298 (0.0)
Magnesium	3	0/288 (0.0)	3/289 (1.0)	25/288 (8.7)	1/289 (0.3)
	4	4/286 (1.4)	4/285 (1.4)	1/286 (0.3)	0/285 (0.0)
	5	10/286 (3.5)	4/285 (1.4)	1/286 (0.3)	1/285 (0.4)
	6	5/286 (1.7)	5/290 (1.7)	0/286 (0.0)	0/290 (0.0)
Calcium	3	0/276 (0.0)	2/282 (0.7)	9/276 (3.3)	6/282 (2.1)
	4	2/274 (0.7)	1/278 (0.4)	4/274 (1.5)	6/278 (2.2)
	5	0/274 (0.0)	0/278 (0.0)	3/274 (1.1)	4/278 (1.4)
	6	0/274 (0.0)	1/283 (0.4)	4/274 (1.5)	2/283 (0.7)
Creatinine	3	2/266 (0.8)	2/270 (0.7)	12/266 (4.5)	16/270 (5.9)
	4	0/263 (0.0)	1/266 (0.4)	19/263 (7.2)	15/266 (5.6)
	5	3/264 (1.1)	2/265 (0.8)	10/264 (3.8)	10/265 (3.8)
	6	1/264 (0.4)	0/272 (0.0)	18/264 (6.8)	10/272 (3.7)
eGFR	3	26/199 (13.1)	25/224 (11.2)	0/199 (0.0)	0/224 (0.0)
	4	25/198 (12.6)	27/220 (12.3)	0/198 (0.0)	0/220 (0.0)
	5	11/198 (5.6)	28/219 (12.8)	0/198 (0.0)	0/219 (0.0)
	6	21/199 (10.6)	24/224 (10.7)	0/199 (0.0)	0/224 (0.0)
Urea	3	45/267 (16.9)	37/274 (13.5)	1/267 (0.4)	2/274 (0.7)
	4	14/263 (5.3)	7/269 (2.6)	4/263 (1.5)	4/269 (1.5)
	5	5/265 (1.9)	5/269 (1.9)	7/265 (2.6)	6/269 (2.2)
	6	9/264 (3.4)	7/274 (2.6)	6/264 (2.3)	9/274 (3.3)

Source: DB7 Statistics review

In the split dose study (2009-01), 30 subjects (Table 22) had potassium shifts from normal to low on the day of colonoscopy, with a more events in the PICOPREP arm (19 vs. 11). The average change in potassium for these 19 subjects in the PICOPREP arm was only 0.63 mmol/L and for the 11 HalfLytely subjects the shift was a similar 0.61 mmol/L.

A similar analysis of sodium showed that the 11 PICOPREP subjects in the split dose study who had a shift from normal to low sodium at Visit 3 had a change of 7.1 mmol/L compared to 6 mmol/L for the 3 HalfLytely subjects.

Renal Function Analysis

An analysis of renal function using creatinine and eGFR was performed for subjects in both trials (combined data) across study visits. The purpose of this analysis was to investigate further the observation that some subjects had abnormally high serum creatinine at Day 30 but normal creatinine values on previous visits and at baseline.

Table 24 presents the increase in mean creatinine at Visit 3 for those subjects normal at baseline and abnormally high values at Visit 3 (above the laboratory-supplied reference ranges.

Table 24. Mean increase in creatinine for subjects with normal baseline creatinine according to Visit 3 shift (by treatment arm)

Treatment	Shift category in Visit 3 creatinine	n	Mean Increase in Creatinine from baseline (mg/dl)
HalfLytely	Normal at baseline to High at Visit 3	29	**0.13**
PicoPrep		17	**0.19**
HalfLytely	Normal at baseline to Normal	505	0.02
PicoPrep		505	0.02

Visit 3 = Day of colonoscopy

The data presented in Table 24 suggest that a small subgroup of subjects had relatively small increase in their serum creatinine on the day of colonoscopy (Visit 3), possibly due to dehydration.

Table 25 presents the mean increase in creatinine at Day 30 (Visit 6) for subjects who had normal creatinine values at baseline and on the day of colonoscopy – but above the reference range on Day 30. The number of subjects is small.

Table 25. Normal Creatinine at Visit 3 (Day of Colonoscopy) and Above Reference Range at Visit 6 (Day 30)

	n	Mean Creatinine increase from baseline (mg/dl)
HalfLytely	14	0.15
PicoPrep	22	0.24

Table 26 presents the serum creatinine changes across study visits for those subjects identified in Table 25 above. Notable is that the mean increase in creatinine appears to "spike" only at the Day 30 visit.

Table 26. Creatinine Values (mg/dl) across study days for subjects with Normal Creatinine at Visit 3 (Day of Colonoscopy) and Abnormal High creatinine at Visit 6 (Day 30)

	n	Day of Colonoscopy	24-48 hours	Day 7	Day 30
HalfLytely	14	0.004	0.02	0.05	0.15
PicoPrep	22	0.02	0.05	0.06	0.24

However, when examining the mean change in eGFRs in the same subjects, there is an apparent trend in decreasing eGFR over time that is more apparent in the PICOPREP arm (Table 27).

Table 27. eGFR [estimated glomerular filtration rate (mmol/L)] across study days for subjects with Normal Creatinine at Visit 3 (Day of Colonoscopy) and Abnormal High creatinine at Visit 6 (Day 30)

	n	Day of Colonoscopy	24-48 hours	Day 7	Day 30
HalfLytely	14	-1.5	-4.1	-4.3	-18.2
PicoPrep	22	-4.6	-6.2	-12.2	-29.8

A review of the individual data for these subjects did not reveal a clear trend in individual subjects' eGFR. The trend appears most evident in the mean values for this subgroup. A review of the adverse event listings in these subjects did not identify a consistent trend in AEs associated with changes in creatinine. The clinical significance of these changes is unknown.

Analysis of Adverse Events Related to Electrolytes Shifts

An information request was sent to the Applicant on May 11, 2012 requested a tabulation and presentation of all adverse events, including serious, for subjects who had shifts outside of normal range for sodium, potassium, chloride, calcium, magnesium and creatinine. A review of this data revealed no specific or more frequent adverse events occurring in these subjects. 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 clinical review).

In addition, a review of subjects who had the most significant shifts in laboratory electrolyte values also did not reveal any unexpected or significant AEs occurring in these subjects. One subject in the PICOPREP arm of Study 2009-01 (subject #108-012), a 70 year old woman, had a 19 mmol/L decrease in sodium (140 to 121 mmol/L) with concurrent nausea and vomiting on day of colonoscopy requiring IV Zofran. Patient also had shifts in chloride (101 to 81mmol/L) suggesting that the vomiting may have contributed to the event.

The clinical reviewer concluded that the adverse events observed in the electrolyte abnormality groups were consistent with the events observed in general within the study.

As noted in the DB7 statistical review, laboratory parameters that differed between groups in both trials include albumin, AST, chloride and magnesium, while the following parameters differed in trial 2009-01 but not 2009-02: urea, potassium and sodium. At the completion of both trials the initial imbalances that were observed resolved, as presented in Table 28.

Table 28. Incidence of abnormal values for laboratory parameters at the day of the colonoscopy (visit 3) and at the last follow-up visit (visit 6) among patients with normal baseline values

		2009-01		2009-02	
Laboratory Parameters	**Visit**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**
Potassium	*3*	26/260 (10.0)	16/268 (6.0)	13/274 (4.7)	14/271 (5.2)
	6	13/284 (4.6)	10/278 (3.6)	8/275 (2.9)	11/284 (3.9)
Sodium	*3*	11/298 (3.7)	5/295 (1.7)	3/286 (1.0)	3/295 (1.0)
	6	3/299 (1.0)	5/291 (1.7)	1/284 (0.4)	1/296 (0.3)
Chloride†	*3*	11/301 (3.7)	1/298 (0.3)	3/287 (1.0)	0/297 (0.0)
	6	2/302 (0.7)	3/294 (1.0)	0/285 (0.0)	0/298 (0.0)
Magnesium†‡	*3*	34/294 (11.6)	0/294 (0.0)	25/288 (8.7)	4/289 (1.4)
	6	8/296 (2.7)	3/290 (1.0)	5/286 (1.7)	5/290 (1.7)
Urea†	*3*	60/287 (20.9)	33/276 (12.0)	46/267 (17.2)	39/274 (14.2)
	6	17/287 (5.9)	12/272 (4.4)	15/264 (5.7)	16/274 (5.8)
Albumin†	3	28/294 (9.5)	13/289 (4.5)	16/277 (5.8)	8/283 (2.8)
	6	6/295 (2.0)	3/285 (1.1)	1/275 (0.4)	3/284 (1.1)
AST	3	15/255 (5.9)	9/265 (3.4)	19/272 (7.0)	10/265 (3.8)
	6	6/277 (2.2)	5/275 (1.8)	5/271 (1.8)	10/277 (3.6)

†-95% CI for risk difference at visit 3 excludes 0 in trial 2009-01;
‡-95% CI for risk difference at visit 3 excludes 0 in trial 2009-02.
Visit 3—day of the colonoscopy; Visit 6—28 days after follow-up.
Source: DB7 statistical review

I concur with the DB7 statistical conclusions that while there were differences between PicoPrep and HalfLytely in selected laboratory parameters collected on the day of the colonoscopy, these differences corrected prior to the completion of follow-up, indicating that imbalances were not present for a prolonged period.

Based on review of collected adverse event data, there were no notable imbalances between PicoPrep and HalfLytely. However, the DB7 statistics reviewer also states that the quality of the safety data may be of concern given the possibility of under-reporting and selected reporting of commonly occurring adverse events. He also recommended that

the product label should state that the true risks of the commonly occurring adverse events (those associated with these products) are likely to be larger than what was reported in the two pivotal trials. In addition, the safety stats review felt that the product label should explicitly detail the adverse event collection strategy used in both trials and caution against comparing reported rates of commonly reported adverse in the PicoPrep label against those in other bowel preparation product labels. The reviewer has proposed wording for the label to reflect his conclusions and these revisions are currently under review.

In addition, I recommend that the electrolyte shifts are adequately presented and described within the label.

Other Safety Assessments

Orthostatic Changes

The clinical reviewer reviewed vital sign trends, individually clinical significant abnormalities, and changes over time and no clinically important findings were seen in her analysis. This includes orthostatic blood pressure measurements taken on the day of colonoscopy.

A summary of orthostatic change in vital signs at Visits 3, 4, and 5 for Studies FE2009-01 and FE2009-02 combined is presented in Table 29.

Table 29. Orthostatic Change in Vital Signs (Safety Analysis Set)

Variable (Criteria)	PICOPREP N = 601			HalfLytely N = 600		
	Visit			Visit		
	3	4	5	3	4	5
Any Orthostatic Change	(N = 598)	(N = 592)	(N = 593)	(N = 598)	(N = 590)	(N = 593)
Decrease in SBP or DBP of ≥20 mmHg and/or an increase in pulse rate of ≥15 bpm from supine to standing	124 (20.7)	94 (15.9)	90 (15.2)	122 (20.4)	77 (13.1)	73 (12.3)
SBP or DBP (mmHg)	(N = 598)	(N = 592)	(N = 593)	(N = 597)	(N = 590)	(N = 593)
Decrease of ≥20 mmHg from supine to standing	32 (5.4)	26 (4.4)	19 (3.2)	28 (4.7)	17 (2.9)	15 (2.5)
Pulse rate (bpm)	(N = 598)	(N = 592)	(N = 592)	(N = 598)	(N = 591)	(N = 593)
Increase of ≥15 bpm from supine to standing	106 (17.7)	70 (11.8)	73 (12.3)	100 (16.7)	65 (11.0)	61 (10.3)

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure
Source: Table 6-3, page 52, Integrated Summary of Safety

Orthostatic changes were comparable between the two treatment arms in the combined analysis. Approximately 20% of subjects in both arms had orthostatic changes, explained predominantly by increases in pulse rate ≥15 bpm. This reviewer recommends that this data is presented within the label, with possible instruction for physicians to consider

evaluating the patient for signs of hypovolemia and dehydration, taking corrective action as needed.

ECG Changes

The clinical reviewer also presented findings on ECG data collected during the trial. She notes the following:

> 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. No new clinically relevant morphological changes were observed.

She also noted that these ECG evaluations are limited in ruling out QT prolongation in light of current standards for the design and conduct of a TQT study.

Table 30 presents the results of the ECG evaluation with regards to the QT interval analysis. At Visit 3, day of colonoscopy, similar small increases from baseline were seen in both treatment arms, PICOPREP 8.7msec and HalfLytely 6.8msec.

Table 30. Mean Changes from Baseline and Proportions of Subjects Who Met Outlier Criteria for QT, QTcF, and QTcB Intervals

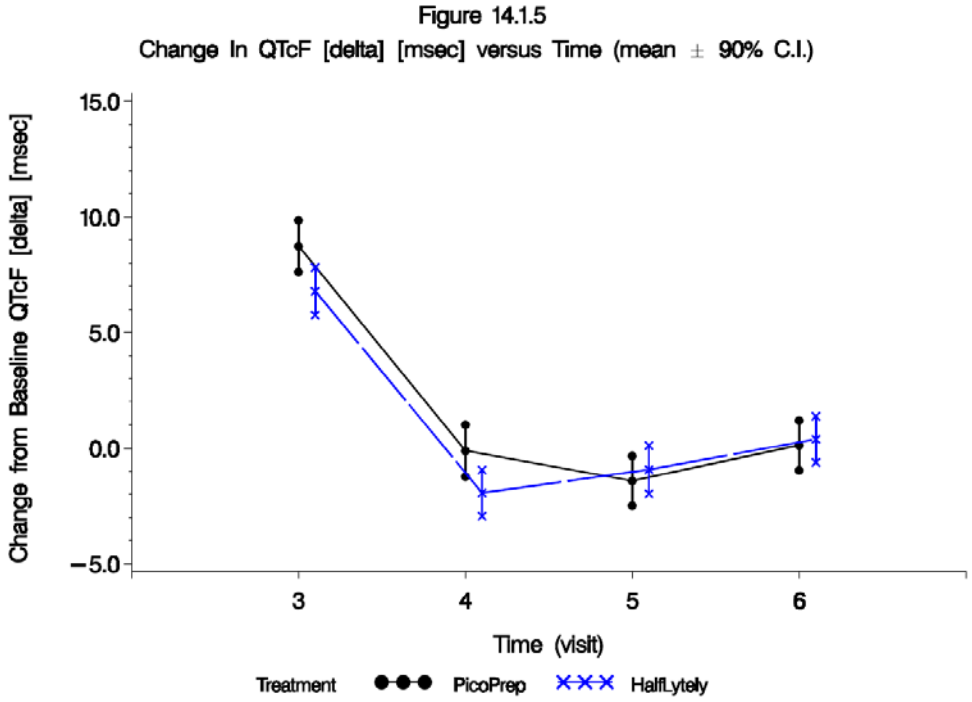
QT Interval	PICOPREP	HalfLytely
Time-Averaged	**(N = 600)**	**(N = 600)**
Mean change from baseline (ms)	-6.4	-6.1
New >500 ms, n (%)	1 (0.2)	1 (0.2)
QTcF mean change from baseline (ms)	0.2	0.3
QTcF new >500 ms, n (%)	1 (0.2)	1 (0.2)
QTcF new >480 ms, n (%)	3 (0.5)	2 (0.3)
QTcF 30-60 ms, n (%)	15 (2.5)	11 (1.8)
QTcF >60 ms, n (%)	1 (0.2)	0
QTcB mean change from baseline (ms)	3.6	3.7
QTcB new >500 ms, n (%)	1 (0.2)	0
QTcB new >480 ms, n (%)	9 (1.5)	8 (1.3)
QTcB 30-60 ms, n (%)	43 (7.2)	40 (6.7)
QTcB >60 ms, n (%)	1 (0.2)	2 (0.3)
Morphology		
New abnormal U wave, n (%)	0	1 (0.2)
Visit 3 Time Point	**(N = 595)**	**(N = 598)**
QT mean change from baseline (ms)	4.2	5.2
QTcF mean change from baseline (ms)	8.7	6.8
QTcB mean change from baseline (ms)	11.1	7.6

Abbreviations: QTcF = Fridericia correction; QTcB = Bazett correction
"new" meant not present at baseline, i.e., at any evaluation pre-dose, and only seen post-baseline.

Source: Table 6-6, Module 5.3.5.3.2, Integrated Summary of Safety

Figure 1 presents the change in QTcF from baseline over the three visits, again showing a similar pattern between the PICOPREP and HalfLytely arms. However, the nature of the trend, with a peak change most proximal to study treatments (bowel cleansing) and a subsequent resolution over time (similar in both arms), suggests a possible relationship to the physiologic effects of the bowel prep regimens.

Figure 1. Mean Change in QTcF. Mean Change from Baseline by Treatment Group for all time points on treatment- Protocols 2009-01 and 2009-02 combined



Source: Figure 3-14, ECG Cardiac Safety Final Report

By way of historical comparison, the clinical review of the Visicol NDA [#21097, August 2000], having the original tradename of "Diacol," describes the ECG analyses investigating the potential for QT prolongation, as such:

> "…the change in mean heart rate or PR interval in either Diacol- or NuLYTELY-treated patients was insignificant. In the Diacol 60 g group (301 and 302), the mean increase in QTc (16.6 msec) and QT (11.5 msec) at Visit 1 were significantly greater than the QTc (6.8 msec) and QT (4.9 msec) mean changes in the NuLYTELY group. At Visit 2 were comparable to baseline values in all treatment groups." [sic]

At the time of Visicol (Diacol) review, FDA requested an outside expert to perform correlation analyses between prolonged QT intervals [using the Bazzet correction (QTcB)] and changes in serum electrolytes. The outside expert noted [as per the clinical review] that, "correlation's were found between serum in serum K and Ca and the QTc at Visit 1 in patients who took Diacol" [sic] and concluded that, "[t]hese findings suggest that changes in serum levels of K and Ca are the most important cause of QT interval prolongation following Diacol administration. The temporal pattern of QT the data also support this conclusion: by Visit 2, when the electrolytes were essentially back to baseline, the QTc behaved likewise." [sic]

Given these historical findings and the data available in the PICOPREP NDA, it is likely to be expected that electrolyte shifts caused by the use of bowel prep regimens could potentially result in prolongation to the QT interval.

Table 31 presents the correlation analysis requested by Ferring between changes in potassium, magnesium and calcium and changes in QT interval. Notable is the significant correlation between changes in serum calcium (not free) and QTcF across Visits 3 and 4 in both treatment arms.

Table 31. Correlation Between Change From Baseline in QT Variables and Change from Baseline in Selected Laboratory Variables By Visit (All Randomized Patients)

Visit	Treatment	Change from Baseline in QT Variable	Correlation With Change from Baseline:	n	Pearson Correlation Coefficient	Test of Significance of Correlation 2-sided p-value *a
3	PicoPrep	QT	Potassium (mmol/L)	558	0.052	0.220
			Magnesium (mmol/L)	588	0.062	0.131
			Calcium (mmol/L)	589	-0.091	0.027 *
		QTcB	Potassium (mmol/L)	558	-0.099	0.020 *
			Magnesium (mmol/L)	588	0.037	0.377
			Calcium (mmol/L)	589	-0.104	0.011 *
		QTcF	Potassium (mmol/L)	558	-0.051	0.228
			Magnesium (mmol/L)	588	0.060	0.148
			Calcium (mmol/L)	589	-0.127	0.002 *
	HalfLytely	QT	Potassium (mmol/L)	566	0.108	0.010 *
			Magnesium (mmol/L)	594	0.121	0.003 *
			Calcium (mmol/L)	594	-0.070	0.088
		QTcB	Potassium (mmol/L)	566	-0.120	0.004 *
			Magnesium (mmol/L)	594	-0.005	0.904
			Calcium (mmol/L)	594	-0.103	0.012 *
		QTcF	Potassium (mmol/L)	566	-0.044	0.297
			Magnesium (mmol/L)	594	0.056	0.172
			Calcium (mmol/L)	594	-0.119	0.004 *

Visit	Treatment	Change from Baseline in QT Variable	Correlation With Change from Baseline:	n	Pearson Correlation Coefficient	Test of Significance of Correlation 2-sided p-value *a
4	PicoPrep	QT	Potassium (mmol/L)	585	0.065	0.116
			Magnesium (mmol/L)	587	0.128	0.002 *
			Calcium (mmol/L)	587	-0.065	0.116
		QTcB	Potassium (mmol/L)	585	-0.166	0.000 *
			Magnesium (mmol/L)	587	-0.000	0.999
			Calcium (mmol/L)	587	-0.083	0.044 *
		QTcF	Potassium (mmol/L)	585	-0.102	0.014 *
			Magnesium (mmol/L)	587	0.061	0.143
			Calcium (mmol/L)	587	-0.095	0.021 *
	HalfLytely	QT	Potassium (mmol/L)	586	0.112	0.007 *
			Magnesium (mmol/L)	588	0.182	0.000 *
			Calcium (mmol/L)	588	-0.081	0.051
		QTcB	Potassium (mmol/L)	586	-0.083	0.044 *
			Magnesium (mmol/L)	588	0.064	0.119
			Calcium (mmol/L)	588	-0.052	0.211
		QTcF	Potassium (mmol/L)	586	-0.011	0.784
			Magnesium (mmol/L)	588	0.141	0.001 *
			Calcium (mmol/L)	588	-0.085	0.039 *

N = number of patients in the specified category.
*a : p-value < 0.05 indicates significant correlation between variables.
Source: Response to Information Request dated 6/19/2012, Table 4.4

In my view, further evaluation of the potential for PICOPREP to cause QT prolongation is not needed, in part due to it being a member of a class of agents (osmotic bowel

cleansing agents) known to cause electrolyte disturbances as well as the discussions surrounding this issue in Section 5 of my review. I therefore disagree with the recommendations noted in Dr. Zana Marks clinical review with respect to the need for a TQT Study.

Review of Post-Marketing Data

General Overview

Refer to Dr. Zana Marks' review for a detailed overview of data available from Periodic Safety Update Reports covering post-marketing availability back to 1990. I agree with Dr. Marks' conclusion that the safety profile of PICOPREP appears generally consistent with the known risks and adverse events reported for similar products in this drug class. However, 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.

Ischemic Colitis

Ischemic colitis is a rare adverse event that may be associated with the use of osmotic bowel preparations. Ischemic colitis emerged as a safety signal in preparations combining bisacodyl + PEG-ELS as a bowel cleansing agent where the amount of bisacodyl was ≥ 10 mg.

There have been no reports of ischemic colitis in either clinical trial study population for this NDA submission.

DGIEP requested that OSE provide an analysis and summary of the AERS data for sodium picosulfate containing products (i.e., approved outside the U.S.), specifically for ischemic colitis.

The AERS search retrieved 5 reports. 4 reports were excluded due to "No evidence of ischemic colitis" (n=2) and "Product not used for bowel prep" (n=2). One case of ischemic colitis was identified in an elderly patient with history of cardiovascular disease, receiving colonoscopy for unknown indication. The contribution of the suspect drug to ischemic colitis is difficult to ascertain given the underlying medical history of ischemia and co-administration of other drugs that may contribute to the adverse event of interest.

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.

9. Advisory Committee Meeting

No Advisory Committee meeting was held to discuss this application.

10. Pediatrics

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 submission was considered by the Pediatric Review Committee (PeRC) on 5/30/2011, and an initial agreement was reached between PERC and DGIEP regarding the pediatric plan. However, following the 5/30 PERC, it was decided that a "standard of care" comparator should be incorporated into the pediatric trials to better inform safety. In addition, there were ongoing discussions regarding whether or not to waive studies in children <1 year old since it was felt that bowel preparation could be achieved with clear liquids alone not only in pediatric patients less than 6 months of age, but instead up to 1 year of age. Therefore the initial age cutoff of <6 months for the waiver was raised to <12 months. These changes were agreed to by the PERC on July 11, 2012.

The following represents the review team's proposal at the time of finalization of my review and may be subject to change:

> We are waiving the pediatric study requirement for ages birth to 12 months because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.
>
> We are deferring submission of your pediatric study for ages 12 months (b) (4) for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

The following PREA studies will be requested in 3 age groups: children ages 12 months to <2 years, ages 2 years to <9 years and ages 9 years to 16 years:

> Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children

ages *[inserting each age group noted above]*. This study will include PK assessments.

Dosing Considerations

As noted in the clinical review, 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 (see Dr. Marks' clinical review for details). A Request for Information was sent to the Applicant on May 01, 2012 requesting an explanation for how the pediatric doses of the products approved in Canada and the United Kingdom were established. However, as described in Dr. Mark's clinical review, no further studies were required in EU since the drug substance had been sold in an EU country for at least 10 years ("well established use" EU directive), and because the available literature provided the necessary level of evidence to support the product having a recognized efficacy and an acceptable level of safety.

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.

Subsequent to the Canadian approval, Turner and colleagues[5] 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.

In summary, although the PICOPREP formulation is approved in other countries with pediatric dosing, the data supporting these doses in children may not be sufficient to preclude actual dose exploration studies in children. Since the applicant has not provided adequate data to support the proposed dosing, then the PREA studies should require dose exploration. The language for the PREA PMRs is currently ongoing at the time of this review.

Additional juvenile toxicity (animal) studies may be requested by the NonClinical review team pending future submission and review of the pediatric protocols; however a nonclinical study is currently not recommended.

[5] 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.

11. Other Relevant Regulatory Issues

505(b)(1) to 505(b)(2) Conversion

During the later course of the NDA review, it was determined that in order to comply with 21 CFR 300.50 ("the combination rule"), the Division would need to rely on published literature. The Division was given guidance from ORP that any information necessary to comply with the combination rule is considered information necessary for approval. Therefore, the reliance on such literature makes this application a 505(b)(2).

ORP and OCC agreed reached an agreement with DGIEP that:

- DGIEP's reliance on literature to support its decision not to require factorial studies was reasonable and fulfills the requirements of the combination policy;
- that fulfilling the policy is essential to approval of this combination product; and
- that reliance on the literature makes this a 505(b)(2) application.

Clinical Contribution of PICOPREP Components

The following is information from published literature that the review team is citing as evidence that it would be unethical to conduct a full factorial study (and impractical to fully implement in my view).

Prior to development of PEG-based bowel cleansing products, interventions based upon differing mechanisms of catharsis were combined in an effort to optimize bowel cleansing. For example, dietary alteration (clear liquid and/or low residue diets of 3-5 days duration) was combined with all of the following: osmotic laxatives, stimulant laxatives and tap water enemas. Ingestion of large volumes of clear liquids or water was also included in these regimens and is still commonly used today for bowel preps with hyperosmotic agents.

In light of the development history of bowel prep regimens, requiring a "full" factorial study raises serious ethical concerns, particularly in light of the negative impact on a patient who undergoes an inadequate bowel preparation for colonoscopy. Further, such full factorial studies likely would be impractical in many cases, as the clinical contribution of the increased intake of clear liquids used as part of the bowel prep regimen, including even prescribed dietary modifications, would require factorial studies impractical or unfeasible by their design.

Colon cancer screening with colonoscopy is performed to detect not only cancer, but pre-malignant lesions, i.e., adenomatous polyps. Detection and removal of these lesions has been shown to prevent future development of colon cancer.[6] Adequate visualization of

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

the colonic mucosa is key to identification and removal of these lesions. Lesions missed during colonoscopy can result in the development of interval colon cancers between screening endoscopies. These malignant tumors arise from lesions that were likely missed in the prior screening examination[7,8]. In addition, a subtype of polyps, serrated polyps, are flat, which makes them particularly challenging to visualize. Without an adequate bowel preparation there is a higher likelihood that such lesions could be missed. Therefore, a patient subjected to a bowel preparation suspected to be inadequate at study initiation (such as in a multi-arm factorial study) would place that patient at increased risk of undergoing a procedure in which a polyp or malignancy is missed. Additionally, certain concerns are raised by the colonoscopy procedure itself which usually requires sedation; both the procedure and sedation are associated with risks of serious adverse events. Exposing a patient to such risk, while knowing that that patient likely will have undergone an inadequate bowel preparation, raises serious ethical concerns.

In order to determine whether a full factorial study would be ethical in light of the concerns raised above, the Division examined the literature for evidence regarding the adequacy of each component of PICOPREP and what is known about the efficacy of each component used as a single agent. The lower bounds of the 95% confidence intervals for the proportion of successful preps (excellent + good) for various recently approved bowel preparations were reviewed. Based on a review of approved bowel prep regimens, it appeared that in order to conclude that a bowel prep agent was not potentially inferior to approved products; the lower bound of the 95%CI should be no less than 70% for a same day prep administration schedule, and no less than 80% for a split dose administration schedule.

The publications in the Table 35 (Appendix) were identified by DGIEP as providing evidence for the efficacy of the individual components, sodium picosulfate and magnesium citrate, in the setting of colonoscopy. Because single agent sodium picosulfate colonoscopy studies were not identified, and because bisacodyl and picosulfate share the same active metabolite, the Division relied upon available literature on the use of bisacodyl in bowel preparation for colonoscopy. Relative exposures to the active metabolite of sodium picosulfate compared to that from bisacodyl are included in the table.

Two-sided 95% CIs were calculated based on the proportion of patients who were identified as having a good or excellent prep for each publication. Three confidence intervals were calculated: The first was based on the actual number of patients with the good or excellent response divided by the actual number in the treatment arm. Two other "adjusted" confidence intervals were calculated based on exploratory projections assuming that the same response rate would have been observed in a larger sample size. This exploration was pursued in light of the very small sample size in some of these studies.

[7] Leung et al, Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointestinal Endoscopy, Vol. 71, No 1:2010, 111-117.
[8] Cohen, Lawrence, Split-dosing of bowel preparations for colonoscopy: an analysis of its efficacy, saety, and tolerability, Gastrointestinal Endoscopy Vol. 72, No. 2:2010, 406-412.

Reader is referred to Table 35 for a tabulation of the published literature used to evaluate the adequacy of using bisacodyl and magnesium citrate alone as bowel preps

All 4 bisacodyl publications studied bisacodyl doses higher than the bisacodyl 14 mg dose that is expected to produce the same amount of active metabolite as sodium picosulfate contained in PICOPREP. In addition, these studies utilized other means of cleansing the colon, including dietary changes of variable durations. Enemas were utilized in all treatment arms of 2 of the studies (Rasmussen et al. and DiPalma et al.); however, it is generally accepted that enemas would not be expected to adequately cleanse the right colon. In DiPalma et al., the bisacodyl was combined with a magnesium citrate dose that is lower than that present in the sodium picosulfate/magnesium citrate products subject to this review.

The Wang et al. publication did not report "good + excellent" bowel prep outcomes, however proportions of "very good + good" were. The authors also included a category of "average." Inclusion of this category was also explored but it is unclear what this category is but could be comparable to the more commonly utilized label in the publications, "fair." For this reason, even though including "fair" was explored, the Division did not rely on that analysis for decision making regarding evidence of efficacy.

The lower bound of the 2-sided 95% confidence intervals (binomial) around the point estimate for proportion of responders ("good" + "excellent" preps) treated with bisacodyl was less than 70%, with one exception in the exploratory calculations estimating 95% CIs based on larger sample sizes. In DiPalma et al., the lower bound of the 95% CI in the exploratory calculations was >70% (73% and 74%); however, these were exploratory calculations. In addition, this study arm also incorporated magnesium citrate and an enema the morning of the colonoscopy, procedures that would like improve the observed treatment benefit. The results of the DiPalma et al. study was included in the estimation of treatment benefit for bisacodyl alone, because the magnesium citrate dose was lower than that in PICOPREP; however this factor and the exploratory derivation of the confidence intervals in question makes this observation unreliable for a decision regarding the ethics of bisacodyl as a single agent in a factorial trial. The Wang et al. publication had an a lower bound of the confidence interval that reached 70 in one of the exploratory calculations, however, this occurred only in one of the analyses that included the "average" rating in the responder definition. The concern about including this category in the analysis was presented above.

None of the 3 publications of magnesium citrate utilized the magnesium citrate dose present in solution for PICOPREP. In 2 studies, the dose was exceeded, and in DiPalma et al., it was less. In addition, other means of cleansing the colon were utilized. All utilized dietary changes of variable durations. Enemas were utilized in one (DiPalma); however, enemas would not be expected to cleanse the right colon as mentioned above. In DiPalma, the magnesium citrate (lower dose) was combined with senna (a stimulant laxative). The nonrandomized audit study reported by Vradelis et al. also included an

arm in which the magnesium was combined with senna (the comparator arm was magnesium citrate only).

The lower bound of the 95% confidence intervals around the point estimate for proportion of responders (defined as good + excellent preps) treated with magnesium citrate was < 70% in all of the "nonexploratory, unadjusted" confidence intervals, with the exception of Berkelhammer et al. and the magnesium plus senna arm in Vradelis, et al. However, these 2 studies utilized magnesium citrate doses that exceeded that derived from PICOPREP in solution, and one of the study arms in Vradelis et al. that had more favorable outcome (lower bound 95% CI >70%) also exposed subjects to the stimulant laxative senna. Further, Vradelis et al. was not a randomized trial and the bowel cleansing score designation differs from the other publications. Therefore, despite more "favorable" outcomes observed in these studies, their design and selected magnesium citrate doses provide no evidence that the use of magnesium citrate alone - at the doses produced in PICOPREP - would provide adequate colon cleansing to support the ethical conduct of a full factorial study.

Excluding the Burkelhamer study, the "exploratory adjusted" confidence interval analyses for the magnesium citrate only arms revealed that only the DiPalma publication demonstrated confidence intervals with a lower bound > 70%. This arm also utilized an enema plus low residue diet for 3 days. This exploratory calculation is not consistent with the observation in the magnesium citrate plus senna arm of the same study (which also incorporated enemas), in which a more aggressive diet regimen (clear liquids) was utilized. One would expect that the magnesium citrate/senna arm would have a higher treatment effect; however, the 95% CI lower bound was < 70%. This raises concerns regarding the magnitude of the treatment effect of magnesium citrate in the exploratory calculations. The Division is unable to conclude that it would be ethical to utilize a magnesium citrate alone treatment arm in a factorial study that has the same dose utilized in PICOPREP.

In conclusion, based on available evidence, a full factorial study to support PICOPREP approval where sodium picosulfate or magnesium citrate would be used as monotherapy would be unethical. This is because there is sufficient evidence to suggest, based on the above analyses, that these components could be ineffective alone and place subjects at risk of having inadequate cleansing and colorectal screening on colonoscopy.

Clinical Site Inspections

A request for clinical site inspections was sent to the Division of Good Clinical Practice Compliance, Office of Scientific Investigations on January 4, 2012.

The rationale for the selection of sites is noted below:

Site 101. This site had the largest patient enrollment with more successful outcomes than the other sites for Study FE2009-01.

Site 106. The investigator John Lowe, MD 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. The investigator Arthur Poch, MD is the same investigator for Site # 212 in Study FE2009-02 (Day-Before Dosing). The rationale for the inspection is the same as stated above under Site 106.

The overall assessment of findings and recommendation from the Office of Scientific Investigations concluded that the data from the 3 sites inspected appear reliable and can be used in support of the NDA. Initial observations for Dr. Lowe's Site 106 were based on preliminary review of the EIR. OSI stated in their review dated 6/20/2012 that an inspection summary addendum will be issued if conclusions change upon further review of the EIR.

Table 32. Clinical Inspection Summary

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication	INSPECTION STATUS
Site 101 Gerald Bertinger, MD Hillmont GI, PC 1811 Bethlehem Pike Building C Suite 300 Flourtown, PA19031 215-402-0800	FE2009-01	123	Colon Cleansing in Preparation for Colonoscopy	NAI
Site 106 John Lowe, MD Advanced Research Associates, LLC 5896 S. Ridgeline Drive Suite A Ogden, UT 84405 Tele: 801-409-2040 Fax: 801-409-0440	FE2009-01	109	Colon Cleansing in Preparation for Colonoscopy	*Pending** (Preliminary classification VAI)
Site 107 Arthur Poch, MD Gastro Intestinal Specialists, AMC 3217 Mabel Street Shreveport, LA 71103 Tele: 318-631-9121 Fax: 318-631-9126	FE2009-01	89	Colon Cleansing in Preparation for Colonoscopy	NAI

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
*According to the OSI reviewers, the violation at Site 106 is regarding a simple protocol violation and it will not affect the validity of the data.

Site 106 final classification was pending that the time of finalization of this CDTL memo.

Proprietary Name Review

Division of Medication Error Prevention and Analysis (Office of Medication Error Prevention and Risk Management) performed a review of the proposed proprietary name, Picoprep, and concluded that the name is unacceptable for the following two major reasons, as copied from the PROPRIETARY NAME REQUEST UNACCEPTABLE letter sent to applicant on 4/27/2012:

1) The proposed proprietary name, Picoprep, is orthographically similar to the proprietary names: Loso prep, Pen prep, and Duraprep. We acknowledge that the proposed Picoprep is a prescription drug product, while LoSo prep, Pen prep, and Duraprep are over-the-counter drug products. However, we have determined that this difference in marketing will not prevent errors between these products because postmarketing experience with other drug products demonstrates that name confusion can occur between similarly named over-the-counter drug products and prescription drug products.

2) We find the inclusion of the "Pico-" prefix in your Picoprep name concerning because it a) suggests the name of one, but not all of your active ingredients, and b) it defines a very small quantity.

The applicant submitted a new name, **Prepopik**, which was later found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). The review team in DGIEP did not have objections to the new name.

12. Labeling

Labeling revisions were ongoing at the time of finalization of this memo. The sponsor was sent a revised proposed label on June 12, 2012.

Proposed revisions have been noted in my discussion of other discipline reviews. In brief, the clinical team felt that more detailed data regarding the electrolyte shifts and related adverse events should be incorporated into the label. A description of electrolyte shifts was not proposed in the original label submitted by the Applicant.

(b) (4)

In addition, there was discussion within the review team whether or not the Day Before dosing should be included in the dosing of the product, since there was evidence that a Day Before regimen could result in less effective colon cleansing compared to the Split Dose. At a minimum, should the product be approved, the sponsor should provide language that clearly indicates that the Split Dose regimen is the preferred dosing.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

  The recommended regulatory action is approval of PREPOPIK [PICOPREP] for the proposed indication, contingent on acceptable labeling and agreement on postmarketing commitments or requirements.

- **Risk Benefit Assessment**

  The benefit of PICOPREP for preparation for colonoscopy has been established in the clinical trials.

  As discussed previously in my review, the importance of a high-quality bowel preparation for the detection of colorectal polyps has been demonstrated in several studies. Current clinical recommendations and guidelines stress that the timing of bowel preparation before colonoscopy, including the use of split

dose regimens, can improve the quality of bowel preparation. In a single trial, PICOPREP 2-day split dosing demonstrated superiority to HalfLytely Day Before dosing, admittedly somewhat of an unfair comparison given the known improvement in cleansing with Split Dose regimens.

However, from a benefit:risk standpoint it would seem that colonoscopies for colorectal cancer should use the most effective bowel cleansing agents available. Patient convenience, although important to ensure adequate treatment adherence, seems an insufficient rationale to support the use of a less effective bowel cleansing regimen for an approved product. However, one could argue that there may be circumstances in which an alternative Day Before regimen is the only practical dosing possible.

Therefore, the sponsor has been given the opportunity to address within the label the preference of Split Dosing over Day Before dosing in a manner that is unambiguous. (These negotiations were ongoing at the time of finalization of my review). I recommend that if the Day Before dosing regimen is approved that the label clearly state that it is not the preferred regimen.

The PICOPREP NDA contained an adequate assessment of the safety of the proposed treatment regimen to support approval. Based on what was found in clinical trials and what is known about pharmacologically related products, no unacceptable risks were identified with this product. Warnings and Precautions (section 5) of the label should contain all of the elements of recently approved bowel prep regimens and describe the risks similarly.

As noted previously, I do not recommend a thorough QT study for this product, because such a study would be impractical for this osmotic bowel prep agent and the electrocardiographic changes have been sufficiently evaluated in the NDA. There is evidence that QT prolongation can be expected from significant shifts in electrolytes and the risks of arrhythmias are already described in the label. I therefore disagree with the recommendation noted in Dr. Marks' clinical review with respect to the need for a TQT Study.

Although orthostatic hemodynamic changes between PICOPREP and the approved comparator were similar, the prevalence of such changes (~20%) should be described in the label with adequate precautions noted. Such risks are not isolated to the PICOPREP product per se, but should represent a known and well-described risk of the class (bowel cleansing agents).

My recommendations for a PMR to evaluate further the effect of this product on renal function is discussed separately below.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A Medication Guide is recommended for PICOPREP should it be approved.

- **Recommendation for other Postmarketing Requirements and Commitments**

  Although changes in mean creatinine and eGFR were observed in the first 30 days of the clinical trials, it is not possible at this time to determine if these changes are entirely attributable to dehydration or other pre-renal effects. Observed increases in mean creatinine and eGFR above the normal range in a small number of subjects at study day 30 suggest the possibility of renal injury becoming clinically apparent only at later timepoints. Admittedly these observations on mean changes in creatinine and eGFR were from exploratory analyses and were not of such a degree as to preclude approval of this product.

  However, based on the exploratory analyses available at the time of finalization of my review, I recommend that the Office consider a safety study as a PMR in patients who receive PICOPREP that is designed to evaluate renal function over at least a 6 month period. The objective of such a study would be to determine the rate of new or persistent changes in renal function at timepoints out to 6 months and to identify any associated risk factors. However, further evaluation of the completed studies could provide additional insight into the risk factors associated with renal dysfunction or provide explanations that may be adequate to supplant the need for additional longer term studies (and potentially inform labeling changes).

  PREA PMRs will be required in accordance with the proposal outlined previously in my review for pediatric patients >12 months of age. I recommend dose ranging studies in pediatric patients to evaluate the most appropriate dose (or formulations) across age or weight groups. Before initiating pediatric studies, the sponsor should provide adequate rationale and justification for the proposed dosing in the pediatric population.

- **Recommended Comments to Applicant**

  There are no recommend comments to Applicant.

14. Appendices

Table 33. 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.

Table 34. 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.

Table 35. Published Literature: Bisacodyl and Magnesium Citrate as Bowel Cleansing Agents

Bisacodyl	*Note: 14 mg bisacodyl results in same amount of active metabolite as 20 mg picosulfate*		
Rasmussen, et. al. [Scand J Gastroenterol 2003 (10):1090]	40 mg bisacodyl total dose (exceeds picolax) 10 mg two days prior to colonoscopy + 15 mg the AM prior to colonoscopy + 15 mg the PM prior to colonoscopy [PLUS clear liquids x 2 days; at least 3 enemas the AM of colonoscopy]	53% = 44/82 CI (42, 65) *Exploratory Analyses:* *Adjusted to 107/200* *CI(46,61)* *Adjusted to 161/300* *CI(48, 59)*	Excellent + good, derived from a figure, so some estimates made to derive this percentage and patient numbers
Dipalma et al [Gastroenterology 1984;86:856-60]	40 mg bisacodyl total dose (exceeds picolax) 20 mg the day prior to colonoscopy+ 20 mg the night prior to colonoscopy [PLUS minimum residue diet x 1 day; 240 cc (17g) Magnesium citrate the day prior + enema the AM of colonoscopy	80% = 35/44 CI(65,90) *Exploratory Analyses:* *Adjusted to 159/200* *CI (73,85)* *Adjusted to 238/300* *CI (74,84)*	Excellent + good
Wang, et al [J Chin Med Assoc, 2003; 66:364-365]	30 mg bisacodyl the day prior to colonoscopy + 3000 cc water	38.8% = 19/49 CI(25,54) *Exploratory Analyses:* *Adjusted to 78/200* *CI(32,46)* *Adjusted to 116/300* *CI(33,44)* Very good + good +"Average" = 37/49 =75.5% CI(61,87) *Exploratory Analyses:* *Adjusted to 151/200* *CI(68,81)* *Adjusted to 227/300* *CI(70,80)*	**Very good + good** on a scale that also included "average," poor and bad.
Chen, et al [J Chin Med Assoc, 2009; 72 (8):402-	Biscodyl 6 tablets (30 mg) the night prior to procedure + 2000cc water [PLUS low fiber diet 3 days prior]	34 /136 = 25% CI (17,33) *Exploratory Analyses:* *Adjusted to 50/200* *CI(19,31)* *Adjusted to 75/300* *CI (20,30)*	

Magnesium citrate	**Picolax contains 26.2 g total magnesium citrate in solution**		
Dipalma et al [Gastroenterology 1984;86:856-60]	Magnesium citrate 240cc (17g) the day prior to colonoscopy [PLUS low residue diet x 3 days, including the day prior + enema the night before colonoscopy and in the morning of colonoscopy]	80% = 32/40 CI(64,91) *Exploratory Analyses:* *Adjusted to 160/200* *CI(74,85)* *Adjusted to 240 /300* *CI(75,84)*	Excellent + good
Dipalma et al [Gastroenterology 1984;86:856-60]	Magnesium citrate 240cc (17g) the day prior to colonoscopy [PLUS clear liquid diet x 3 days, including the day prior + enema the night before colonoscopy and in the morning of colonoscopy + Xprep, 240cc senna]	69% =44/64 CI(56,80) *Exploratory Analyses:* *Adjusted to 138/200* *CI(62,75)* *Adjusted to 206/300* *CI(63,74)*	Excellent + good
Berkelhammer et al [Gastrointestinal Endoscospy, 2002, 56:89-94]	Magnesium citrate 300cc (17g) x 3 (TOTAL of **51g**) on the day prior to colonoscopy [PLUS clear liquid diet the day prior]	94%* = 131/140 CI(88,97) *Exploratory Analyses:* *Adjusted to 187/200* *CI(89,97)* *Adjusted to 281/300* *CI(90,96)*	Good +Excellent *the total percentage for combined good+excellent not shown; data presented by colon segment, so used the lowest total percentage, which was 94% for the right colon
Vradelis, et al. [2009, 15 (14):1759-63]	Magnesium citrate 35g split dose. [PLUS low residue diet followed by a clear liquid diet]	108/160 = 68% CI(60,75) *Exploratory Analyses:* *Adjusted to 135/200* *CI(61,74)* *Adjusted to 203/300* *CI(62,73)*	**NONRANDOMIZED AUDIT** Good + Satisfactory Satisfactory = small amounts of feces or fluid not interfering with the exam.
Arm 2 of Vradelis, et al	Magnesium citrate 35g split dose + **SENNA** (the day prior). [PLUS low residue diet followed by a clear liquid diet]	148/182 = 81% CI(75,87) *Exploratory Analyses:* *Adjusted to 163/200* *CI(75,87)* *Adjusted to 244/300* *CI(77,86)*	**NONRANDOMIZED AUDIT**

Source: Tabulations and calculations performed by Dr. Donna Griebel

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/s/

ROBERT FIORENTINO
07/14/2012