CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202535Orig1s000

SUMMARY REVIEW

Division Director Review

Date	July 16, 2012
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	202535
Applicant Name	Ferring Pharmaceuticals, Inc
Date of Submission	September 16, 2011
PDUFA Goal Date	July 16, 2012
Proprietary Name / Established (USAN) Name	Prepopik/ (sodium picosulfate, magnesium oxide, citric acid)
Dosage Forms / Strength	Powder for oral solution in a sachet. Each sachet contains sodium picosulfate 10.0 mg, magnesium oxide 3.5 mg, citric acid 12.0 mg
Proposed Indication(s)	Colon cleansing in preparation for colonoscopy in adults
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Zana Marks, MD
Statistical Review	Shahla Farr/Mike Welch, PhD
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder, PharmD
CMC Review/OBP Review	H. Schroff, PhD/R.Bloom, PhD/M. Kowblansky, PhD M.Trehy, PhD/B.J.Westenberger, PhD
Clinical Pharmacology Review	Dilara Jappar, PhD/Sue-Chih Lee, PhD
DSI	Khairy Malek, MD/Susan Thompson, M.D
CDTL Review	Robert Fiorentino, MD, MPH
OSE/DMEPA	Manizheh Siahpoushan/Carol Mena-Grillasca/Zachary Oleszcruk
OB/DB7	Bradley McEvoy, MS, DrPH/LaReeTracy, MA,PhD/ Aloka Chakravarty, PhD
OSE/DPV-1	Christian Cao, MPAS, PA-C
Division of Cardiovascular and Renal Products	Norman L Stockbridge, MD, PhD
OMP/OPDP (Patient labeling)	Latonia Ford
OMP/OPDP/DCDP	Eunice Chng-Davies/Kathleen Klemm
SEALD	Eric Brodsky, MD/Laurie Burke, RPh, MPH

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DB7= Division of Biometrics 7
DMEPA=Division of Medication Errors Prevention and Analysis
DPV = Division of Pharmacovigilance
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management

DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
OMP= Office of Medical Policy
OPDP=Office of Prescription Drug Promotion
SEALD=Study Endpoints and Label Development

1. Introduction

The applicant proposes Prepopik for use as a bowel cleanser prior to colonoscopy. Prepopik contains three active ingredients: sodium picosulfate, anhydrous citric acid and magnesium oxide. It is a powder for oral solution that is packaged in two packets, each of which is dissolved in 5 ounces of water for administration. Each sachet contains sodium picosulfate 10.0 mg, magnesium oxide 3.5 mg, citric acid 12.0 mg. Patients also must consume clear liquid after each of the two doses of Prepopik solution – five 8 ounces drinks after the first dose and three 8 ounce drinks after the second dose (total 2200 cc). Magnesium oxide and citric acid react to create magnesium citrate in solution, an osmotic agent that causes water to be retained within the gastrointestinal tract. The sodium picosulfate is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM, that acts directly on the colonic mucosa to stimulate colonic peristalsis.

The reviewers and CDTL have recommended approval of this NDA and I concur with their recommendation. The major efficacy review issues for this NDA included: 1) whether the applicant and provided sufficient information in the NDA to establish that the combination rule had been fulfilled, and 2) whether the approved label should include the "Day Before" (entire preparative regimen administered the day prior to colonoscopy) evaluated in one of the major trials submitted in support of this NDA. The major safety issues included: 1) whether the eGFR, creatinine and other laboratory data raised sufficient safety concerns to justify requiring a post marketing safety trial, and 2) whether there was evidence of ischemic colitis associated with Prepopik, given that the active metabolite of the picosulfate component of the product is the same as that of the bisacodyl component of HalfLytely and Bisacodyl 10 mg Tablets Bowel prep Kit, which was the active comparator arm of the two major trials submitted to support this NDA. HalfLytely and 10-mg Bisacodyl Tablets Bowel prep Kit is no longer marketed due safety concerns related to ischemic colitis. Finally, the appropriate pediatric development plan that should be required under PREA was carefully considered. A recently approved osmotic colon cleansing product was required to study children down to the age of 6 months, and to include an active control, Nulytely, which carries pediatric labeling down to the age of 6 months. The reviewers evaluated whether the lower age limit of 6 months is appropriate for the pediatric development plan, whether dose finding is necessary in the pediatric population in light of the existence of pediatric labeling for this product in countries outside the US, and whether a Nulytely comparator should also be required for this product's pediatric plan. My review will highlight these review issues.

2. Background

There are a number of osmolar cathartic agents marketed for colon cleansing for colonoscopy and/or surgery. The contents of those agents are summarized in the table below to facilitate a comparison of the specific salt content between Prepopik and other marketed products. Prepopik is packaged in two packets, each of which is dissolved in 5 ounces of water for administration. Each sachet contains sodium picosulfate 10.0 mg, magnesium oxide 3.5 mg, citric acid 12.0 mg. Patients must consume clear liquid after each of the two doses of Prepopik solution – five 8 ounces drinks after the first dose and three 8 ounce drinks after the second

dose (in total 2200 cc). The magnesium oxide and citric acid react to create magnesium citrate in solution (osmotic agent). The dose of magnesium citrate associated with administration of each packet of Prepopik is approximately (b) (4). The sodium picosulfate is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM. BHPM, a stimulant laxative, is the same active metabolite as bisacodyl, which is a component of the Halflytely 10-mg Bisacodyl Tablets Bowel prep Kit comparator arm in the two major trials submitted in this application. Although this Halflytely product was marketed at the time these trials were initiated, it has been removed from the market due to safety concerns related to ischemic colitis. It was removed after the currently marketed Halflytely 5 mg Bisacodyl Tablets Bowel prep Kit was shown to have similar efficacy to the product that contained 10 mg Bisacodyl tablets. The original Halflytely product, which contained 20 mg bisacodyl, was associated with adverse events of ischemic colitis. It was replaced by the product containing biscodyl 10 mg, for which there were also reports of ischemic colitis.

Table 1: Summary of Approved Products and Ion Content

Drug Name	Content	Indication
Oral Sulfate Prep		
Suprep *treatment consists of ingestion of 2- 6 oz bottles*	*Per total 12 oz dose* Sodium Sulfate, 35.02g Potassium Sulfate 6.26 g (2.8g or 72 mEqu K) Magnesium Sulfate 3.2 g (2.66 mMoles) Sodium Benzoate, (b) (4) (b) (4)	colonoscopy
Oral Sodium Phosphate Preps		
Visicol *treatment consists of ingestion of 40 tablets*	*Per tablet* Sodium Phosphate monobasic monohydrate 0.398 g dibasic anhydrous, 1.5 g	Colonoscopy (F/u Day 2-3)
Osmoprep *treatment consists of ingestion of 32 tablets*	*Per tablet* Sodium Phosphate monobasic monohydrate 1.102 g dibasic anhydrous, 0.398 g	Colonoscopy (Day of colonoscopy=last lab) NDA includes comparison to Visicol)
Fleets	Sodium Phosphate	
PEG + Electrolytes		
Colyte *Treatment consists of ingestion of a 4 liter solution*	*Per total 4 liter dose* Sodium Sulfate, 22.72 g (anhydrous) Sodium Chloride, 5.84 g Sodium Bicarbonate, 6.72 g Potassium Chloride, 2.98 g (40 mEqu K) PEG-3350, 240g	Colonoscopy, Barium enema
GoLytely *Treatment consists of*	*Per total 4 liter dose, jug/packet* Sodium Sulfate, 22.74 g/21.5g	Colonoscopy, Barium enema

Drug Name	Content	Indication
ingestion of a 4 liter solution	Sodium Chloride, 5.86 g/5.53 g Sodium Bicarbonate, 6.74 g/6.36 g Potassium Chloride, 2.97g/2.82 g (40 mEqu K) PEG-3350, 236g/227.1 g	Data in the Moviprep NDA No f/u post colonoscopy
Nulytely *Treatment consists of ingestion of a 4 liter solution*	*Per total 4 liter dose* Sodium Chloride, 11.2 g Sodium Bicarbonate, 5.72 g Potassium Chloride, 1.48 g (20 mEqu K) PEG-3350, 420g	Colonoscopy (F/u Day 2-3 in comparison to Visicol)
Moviprep *Treatment consists of ingestion of a 2 liter solution (comparator arm in the phase 3 trials for Suprep)*	*Per <u>total</u> 2 liter dose* Sodium Sulfate, 15 g Sodium Chloride, 5.38 g Potassium Chloride, 2.03 g (27 mEq K) PEG-3350, 200g Sodium Ascorbate, 11.8 g Ascorbic Acid, 9.4	Colonoscopy Last lab day of colonoscopy
PEG + Electrolytes + Bisacodyl *Treatment consists of ingestion of a 2 liter solution*	One 5 mg bisacodyl delayed-release tablet + *Per 2 liter bottle (total dose; 2000cc water reconstitution*) Sodium Chloride 5.6 g Sodium bicarbonate 2.86 g Potassium Chloride 0.74 g 210 grams of polyethylene glycol (PEG) 3350, Flavoring 1 g	Colonoscopy No laboratory assessment in recent supplement. Not clear how assessments performed in original application

FDA issued a Supplement Request Letter on December 10, 2008 under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to manufacturers of <u>oral sodium phosphate</u> products requiring that the labels be revised to include a Boxed Warning to warn of the risk of acute phosphate nephropathy and directing the manufacturers to develop a risk evaluation and mitigation strategy (REMS) that included a Medication guide to alert patients to the risk of acute kidney injury associated with the use of these products and a communication plan to inform healthcare providers likely to prescribe or dispense oral sodium phosphate products, and to conduct a postmarketing clinical trial to further assess the risk of acute kidney injury with the use of these products. The required clinical trial under section 505(o)(3) of the FDCA was "A prospective, randomized, active-controlled trial comparing the risk of developing acute kidney injury in patients undergoing bowel cleansing using (the oral phosphate product) as compared to patients undergoing bowel cleansing using polyethylene glycol (PEG) containing products."

The approved osmotic colon cleansing product labels, not just the oral sodium phosphate products, carry very similar, if not identical, warnings regarding risks of dehydration and

serious fluid and electrolyte adverse effects and their consequences (including seizures and cardiac arrhythmias). Postmarketing safety studies were a condition of approval of a recently approved osmotic colon cleansing product Suprep. (That approval letter states, "We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of ischemic colitis, renal failure or other serious renal disease, seizure disorders, new arrhythmias, or other uncommon but serious adverse events. Available data for other drugs in the same pharmacologic class indicate the potential for these serious risks. Analysis of spontaneous postmarketing adverse events also will not be sufficient to assess the signals of serious risks of aggravation of gout and serious outcomes associated with elevations of creatine kinase related to the use of the drug.")

Regulatory History of Prepopik Development: Key points in the regulatory history in the development of Prepopik are summarized below:

In the April 16, 2009 pre-IND meeting, **t**he Agency provided general agreement with the proposed phase 3 trial designs; however, the Agency stated the non-inferiority margin should be changed from 15% to 9%, additional visits for safety assessments should be incorporated, and measures to better ensure blinding of the colonoscopists were needed (since patients and study coordinators would not be blinded). Of note, the Agency recommended that all colonoscopies should be scheduled as a morning procedure (which reduces the time interval from last dose of same day/day before administered bowel preps like HalfLytely). In addition, the FDA recommended the applicant consider utilizing a split dose regimen control arm in the split dose Prepopik study.

The Agency concurred with the dose selected for study. The Agency recommended a thorough QT study; however, the applicant chose to incorporate ECG monitoring in the clinical trials.

In addition, the Agency requested evidence that each component of PREPOPIK contributes to the claimed effect. 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.

At the 21 March 2011, Pre-NDA meeting the applicant agreed to evaluate the pharmacokinetics of sodium picosulfate.

At the time that the phase 3 trials were designed the comparator arm, HalfLytely and 10-mg Bisacodyl Tablets Bowel prep Kit with 10 mg bisacodyl was an approved and marketed product. In the interim since the trials' initiation, the comparator product was removed from the market for reasons of safety, as stated above, and a Halflytely product with a lower dose of bisacodyl replaced the Halflytely 10 mg product. Use of the previously marketed Halflytely product as the control arm in the trials that support the NDA under review is acceptable since the basis of removal of the product from the market was not efficacy (the trials were

noninferiority trials), and the safety issue was well defined and could be assessed within the context of this clinical trial and through evaluation of postmarketing data from substantial use outside the US. Evidence of comparable risk of ischemic colitis relative to the Halflytely products that have been removed from marketing would be an issue impacting risk/benefit assessment of Prepopik. See Section 8 Safety of this review, in the subsection Ischemic Colitis, for further discussion of this issue.

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

The CMC reviewer required a number of labeling revisions, which the applicant accepted. These included modifying the established name (b) (4) to 'anhydrous citric acid,' inclusion of all inactive ingredients in the Description section, inclusion of the chemical names, structures, molecular formulae and weight for anhydrous citric acid and magnesium oxide in the Description section, removal of all magnesium citrate information from the Description section, and inclusion of the product's pharmacological/therapeutic class

The applicant provided calculations for environmental assessment and the reviewer determined that the NDA qualified for a categorical exclusion claim.

The Division of Pharmaceutical Analysis (DPA) reviewed and performed the method validation and found it acceptable for quality control and regulatory purposes. However, the DPA "strongly" suggested "inclusion of system suitability requirements in the procedure….to assure that the HPLC is performing adequately to obtain quality data." The CMC reviewer recommended that this comment did not need to be conveyed to the applicant.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical issues that preclude approval. The reviewers determined that the acceptance criteria for the unknown impurities and the total impurities are acceptable. I concur with the reviewers' recommendations for product labeling. Although there were nonclinical studies of sodium picosulfate from the literature on reproductive toxicology submitted for review, the nonclinical reviewers stated they did not rely on this information for their decision. Instead, they relied upon the nonclinical reproductive toxicology studies conducted with the combination product sodium picosulfate, magnesium oxide, and citric acid.

Intestinal mucosal hyperplasia and lymphoplasmacytic infiltrates were observed in histopathology examinations of tissues from animals in the nonclinical rat studies submitted for sodium picosulfate. I discussed these findings with the nonclinical reviewers and they noted that these observations occurred at picosulfate doses that approximated 1800 times the recommended human dose of sodium picosulfate and were not observed in the Prepopik

(combination sodium picosulfate, magnesium oxide and citric acid) nonclinical rat and dog studies.

The reviewers noted that the reproductive toxicology studies in rats did not reveal impaired fertility or harm to fetus. A Segment II, oral (gavage) embryofetal development study in New Zealand white rabbits treated with Prepopik at 230, 460 and 900 mg/kg BID doses resulted in external, visceral and skeletal malformations in the fetuses at 900 mg/kg dose level. Other fetal alterations observed in this study were not considered treatment related. Maternal toxicity was seen at all doses (230, 460 and 900 mg/kg BID), characterized by reduced food consumption, weight loss, dehydration, abortion and/or death. The incidence and severity was dose-related. Similarly, the incidence of abortion in this study was 0, 1, 2 and 8 in the 0, 230, 460 and 900 mg/kg BID groups, respectively. Treatment-related abortions were observed at all dose levels and increased with increasing dose, and were considered to be secondary to poor maternal conditions. The reviewers recommended that the reproductive toxicity data in the product label be limited to the information from the rat studies because the dose level at which the malformations attributed to drug occurred was maternal toxic, resulting in the deaths of 11/20 dams in that dose group. I concur with the recommendation for Pregnancy Category B labeling.

5. Clinical Pharmacology

The Clinical Pharmacology review found the application acceptable for marketing approval as long as labeling recommendations were adequately addressed.

The reviewer summarized the study findings as follows, which is quoted from her review:

"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 even 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%.

In addition to picosulfate and BHPM, serum magnesium level was also evaluated in this study. Following the administration of PREPOPIK, magnesium level increased by approximately 20% compared to the baseline. Peak magnesium concentration was approximately 1.9 mEq/L with Tmax of 10 hour post first dose. However, the magnesium level stayed within the normal range during this study."

The mean half life of the picosulfate in 16 subjects was 7.42 hours (SD 3.157). The mean half life of the active metabolite BHPM could only be evaluated in two subjects and was 15.54 hours (SD 19.488).

The PK parameter data for magnesium are summarized in the table below, which is reproduced from the clinical Pharmacology review. Note that the highest Cmax value for magnesium was 2.3 mEq/L.

Table 2. Pharmacokinetic Parameters for Magnesium

Pharmacokinetic parameter	Unit	Mean (± SD)	Minimum	Median	Maximum
Raw Magnesium					
C_{max}	mEq/L	1.9 (0.2)	1.6	1.9	2.3
C_{max} (first pouch)	mEq/L	1.8 (0.1)	1.5	1.8	2.1
T_{max}	hr	10.0 (4.0)	4.0	10.0	16.1
T_{max} (first pouch)	hr	3.4 (1.1)	1.0	4.0	4.0
AUC_t	hr*mEq/L	84.2 (5.2)	75.3	83.3	97.2
Baseline corrected Magnesium					
C_{max}	mEq/L	0.4 (0.1)	0.3	0.4	0.6
C_{max} (first pouch)	mEq/L	0.3 (0.1)	0.2	0.2	0.4
T_{max}	hr	10.0 (4.0)	4.0	10.0	16.1
T_{max} (first pouch)	hr	3.4 (1.1)	1.0	4.0	4.0
AUC_t	hr*mEq/L	11.4 (3.0)	5.6	11.1	15.4

No substantive drug interactions for the picosulfate component were detected in cultured human hepatocyte studies of CYP enzyme interactions. The reviewer noted a potential for the product as a whole to impact absorption of other concomitantly administered drugs through its cathartic effect (resulting in decreased transit time for the other drug). She also noted that the potential for the magnesium in Prepopik to chelate other drugs and interact with drug transporters were not evaluated. The reviewers noted that the non-US label for this product, which is approved and marketed outside the US, contains language addressing the potential for chelation and concluded this information should also appear in the US label in Section 7 Drug Interactions: "Section 7.2 Potential for Altered Drug Absorption: Tetracycline and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine and penicillamine, should be taken at least 2 hours before and not less than 6 hours after administration of PREPOPIK to avoid chelation with magnesium." I concur.

The Clinical Pharmacology reviewer pointed to concomitant antibiotic use as a chief drug interaction concern, because of the potential for negatively impacting efficacy, since gut bacteria convert the sodium picosulfate into its active metabolite. I concur with including information in the product label regarding this issue in Section 7 Drug Interactions: 7.3 Antibiotics.

A waiver of a thorough QT study had been requested and after reviewing the waiver request the QT/IRT team concluded that thorough QT assessment should be conducted to exclude small effects on QT as the product has systemic bioavailability. I concur with the CDTL and clinical Pharmacology reviewers' expressed concerns regarding the practicality of conducting a thorough-QT study for this product, given the low exposure of picosulfate at therapeutic doses and questions about the ethics of administering supratherapeutic doses. I agree with the

CDTL that the electrolyte shifts from the diarrhea induced by the product would be expected to produce conduction changes. Bowel cleansing products are currently labeled for their potential to cause fluid and electrolyte shifts which can cause serious adverse events, including arrhythmias. I concur that conduct of a tQT study is not justified, for the reasons described.

The applicant conducted serial ECGs as part of the two major trials submitted in support of this NDA. On the day of colonoscopy, QTcF mean change from baseline in the Prepopik treated patients was 8.7 ms vs. 6.8 ms in the Halflytely treated patients. I concur with the CDTL that these relatively small increases in QT interval were likely secondary to the physiological effects of the bowel preparations through their impact of fluid and electrolytes. The CDTL cited the Visicol NDA 21087 review and its commentary on the QT prolongation observed in the safety dataset. These changes were attributed to changes in serum potassium and calcium levels.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted two randomized, controlled trials (unblinded for the subject and site study coordinator) to support the efficacy of Prepopik. Both studies compared Prepopik to HalfLytely and 10-mg Bisacodyl Tablets Bowel prep Kit, an approved PEG plus electrolyte osmotic laxative at the time of trial conduct that has subsequently been withdrawn from the market and replaced by a Halflytely product that contains a lower (5mg) dose of bisacodyl. The two trials differed only by the Prepopik dosing regimen. In both trials the Halflytely was administered entirely on the day prior to the colonoscopy. In Study FE2009-02 (heretofore referred to as Study 02), the two doses/sachets of Prepopik were also administered entirely the day prior to colonoscopy ("Day before regimen"). In Study FE2009-01 (heretofore referred to as Study 01), one dose/sachet of Prepopik was taken the night before colonoscopy and second was administered the following morning, on the day of colonoscopy ("Split dose regimen"). It should be noted that each dose/packet of Prepopik is dissolved in 5 oz of water, and the first dose/packet of Prepopik was followed by 40 oz. of water, and the second by 24 oz. of water (a total of 2520 cc of water). Once prepared, the HalfLytely solution volume is 2000 cc. Dietary instructions for each arm were identical, i.e., clear liquids on the day prior to colonoscopy, and consistent with the approved Halflytely label.

The primary analysis variable in both trials was the proportion of responders/successes. Success was defined by a colonoscopy score (on the 4-point Aronchick Scale) equal to good or excellent (assigned by blinded colonoscopist). "Good" on the Aronchick Scale equals >90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization. An "excellent" score equals >90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization. The scores below "good" on this scale are assigned when there is a mixture of liquid and semisolid stool that could be suctioned and/or washed to allow >90% visualization (fair) or the semisolid stool cannot be adequately suctioned and washed, resulting in <90% visualization (inadequate). The Aronchick Scale appears was designed to

assess/score the degree of cleansing of the overall colon. This scale was not utilized in these trials to assess specific segments of the colon in isolation.

Secondary analyses included evaluation of proportion of responders/successes by individual colon segment (ascending, transverse, descending), which were assessed with a different scale, the 5-point Ottawa scale. The Ottawa scale appears to have been designed to score isolated colon segments, not the overall colon. In these trials cleansing of the ascending colon in isolation, was a key secondary endpoint.

Based on their definitions, the good and excellent categories of the Ottawa scale, combined together, appear narrower in scope of quality of cleansing than the Aronchick combined good and excellent categories. The Ottawa "good" score excludes colonoscopy preparations that resulted in the need for washing and suctioning to adequately visualize mucosa. The Ottawa combined scores of Excellent, Good and Fair appear to be qualitatively similar to the combined Aronchick good + excellent scores. The scale utilized in the clinical trials which supported the approval of HalfLytely, provided in the table below, was not identical to the Aronchick score. The relevance of this difference to this application, in which the primary analysis of the major trials was noninferiority, is discussed below. The clinical review for the approval of the original Halflytely product (20 mg), indicates that the same scale was used in the major trials that supported that application.

Table 3 : Bowel Preparation Cleansing Score for HalfLytely Registration Trials

Cleansing Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional cleansing required
2	Fair	Enough feces or fluid to prevent a completely reliable exam
3	Good	Small amounts of feces or fluid not interfering with the exam
4	Excellent	No more than small bits of adherent feces or fluid

The primary objective of both trials was to demonstrate noninferiority of Prepopik to HalfLytely in overall colon cleansing. The protocol stated that both the ITT and per protocol analysis sets would be utilized for the primary efficacy analysis. If noninferiority (NI) was established, superiority would be tested, utilizing the ITT analysis set. The sample size was calculated based on an estimated responder rate of 85% in both arms, a 9.0% NI margin, 85% power, and a one-sided significance level of 0.025. As the statistical reviewer stated in her review, from an FDA review standpoint, "the NI margin (M2) of 9% will be used for this study, primarily based on clinical judgment, as well as historical precedent with recently conducted phase 3 program that led to the approval of OsmoPrep®, using 10% NI margin Statistical Review, NDA 21-892)." The reviewer pointed out that utilizing 50% of M1 is unacceptably high, in light of the clinical importance of an optimal quality bowel prep for colonoscopy. The placebo response is expected to be quite low, but merely "beating" placebo would be considered unacceptable in clinical medicine. The statistical reviewer for the IND had recommended an even "tighter" NI margin of 4%, "based on allowing a 5% relative decrease from the control," however, that recommendation was not followed by the applicant.

The analysis of the key secondary efficacy endpoint ascending colon cleansing success was specified in the protocol to be a NI analysis assessed by the Ottawa scale, with success/responder defined as ascending colon graded a score of excellent, good or fair. The lower bound of the 97.5% one-sided confidence interval for the difference (Prepopik minus HalfLytely) was set at -9.0% to declare noninferiority. Superiority would be tested if NI was declared. The limitation for setting an evidence-based NI margin is discussed below.

The primary efficacy results are summarized in the tables below, which are reproduced from the Statistical review. The prespecified noninferiority criteria were met in both trials. Superiority was then tested, and in one of the trials (the Prepopik split dose trial) superior efficacy was observed in the Prepopik arm. However, HalfLytely was administered entirely on the day prior to colonoscopy, whereas the second dose/sachet of Prepopik was administered in the morning of colonoscopy in this trial. It has been well documented in the literature that regimens administered more proximal to the time of colonoscopy (split dose regimens) yield superior cleansing to preps administered at a greater time interval from the procedure (entirely the day prior to procedure, referred to in this review as Day Before regimen).

Table 4: Study 01 (SPLIT DOSE PREPOPIK) – Statistical Reviewer's Analysis* - Response Rates and Non-Inferiority Test for the Primary Endpoint (ITT)

Aronchick Scale	**Prepopik Split dose regimen (n=304)**	**HalfLytely (n=295)**	**Difference [Prepopik minus HalfLytely] with 95% CI**
Excellent + Good	**256/304 (84.2%)**	**221/295 (74.9%)**	**9.3% (2.9%, 15.7%)**

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

Table 5: Study 02 (DAY BEFORE DOSE PREPOPIK) – Statistical Reviewer's Analysis* - Response Rates and Non-Inferiority Test for the Primary Endpoint (ITT)

Aronchick Scale	Prepopik (n=294)	HalfLytely (n=300)	Difference [Prepopik minus HalfLytely] 95% CI
Excellent + Good	**244/294 (82.9 %)**	**239/300 (79.7%)**	**3.3% (-3.0%, 10.0%)**

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

The per protocol analyses were consistent with the observed outcome in the ITT analyses.

I concur with the Clinical and Statistical reviewers that the two major trials submitted in this NDA establish that Prepopik is efficacious for bowel cleansing for colonoscopy, based on the analysis of the primary endpoint. Although the scale used to obtain the score for the noninferiority analysis differed from the one used to establish the effectiveness of Halflytely in the registration trials for that product, the scale used in Study 01 and Study 02 appears more stringent in its description of what the colonoscopist observed during the procedure. I do not

think that this change should impact our ability to determine the comparability of the two products. The change of scoring system might have changed the treatment effect associated with Halflytely, relative to placebo, if the Aronchick score had been utilized in its registration trials; however, placebo controlled data were also absent for setting the margin based on that scoring system. Establishing a noninferiority margin based on a true treatment effect relative to placebo has been a recurrent issue discussed in FDA reviews of NDAs for bowel cleansing products, due to the lack of placebo controlled data (with any scoring system). Statistical reviewers have advocated setting a conservative NI margin in order to support a noninferiority claim, and if not met, the clinical reviewers have examined the lower bound of the confidence interval for the observed success rate observed to determine if that rate exceeds what would be reasonably expected with a placebo in this setting. In the current application, the Statistical reviewer was not only satisfied with the observed outcome of the noninferiority analysis, but the split dose regimen of Prepopik was also found to be superior to the HalfLytely 10 mg product (administered entirely the day prior to colonoscopy). Although the latter finding is not unexpected in light of the generally recognized superior quality of split dosing (with last dose administered on the day of colonoscopy) relative to regimens administered entirely the day prior to the procedure, this observation does establish the effectiveness of Prepopik.

A quality measure that has been explored for clinical endoscopy practices is the actual identification of polyps. Target rates of colonoscopies in which adenomas are identified have been proposed as quality measures. Some colon cleansing publications have examined identification of adenomas as an efficacy measure. Polyps were recorded as treatment emergent adverse events in this NDA. These safety data, summarized below, reveal a similar distribution of "colonic polyp", "rectal polyp" and "colon adenoma" detection between arms. (Table is reproduced and modified to show only the neoplasms, from CDTL safety review.)

Table 6 Treatment –Emergent Adverse Events of Polyps (Safety Analysis Set)

Category System -Organ-Class Preferred Term	PREPOPIK N=601 n (%)	HalfLytely N=600 n (%)
Colonic polyp	89 (14.8)	98 (16.3)
Rectal polyp	25 (4.2)	27 (4.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	115 (19.1)	118 (19.7)
Colon adenoma	103 (17.1)	108 (18.0)

Subjects with multiple events in the same treatment-emergent adverse event category are counted only once. Source: ISS Table 3.2.1 Source: Clinical Review

The Statistical reviewer observed that the analyses of the key secondary endpoint, cleansing of the ascending colon (as assessed by Ottawa scale; excellent + good + fair) met the applicant's prespecified criteria for noninferiority of Prepopik in both trials. In addition, subsequent testing of superiority indicated superiority of the Prepopik Split dose regimen in Study 01. These analyses are summarized below (applicant tables presented in the Statistical review). The Statistical reviewer presented her own analysis of the secondary endpoint in Study 01, and

confirmed the applicant's results [Difference = 10%; 95% CI (5%. 16%)]. Her review does not include her analysis of the secondary endpoint of Study 02.

Table 7: Study 01 (SPLIT DOSE PREPOPIK) –Secondary Endpoint: Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale; ITT and PP (Applicant's Study Report)

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.
b. Non-inferior and superior.

Source: Table9-3 of Sponsor's Study Report, Page 51 of 80

Table 8: Study 02 (DAY BEFORE DOSE PREPOPIK) – Secondary Endpoint: Non-inferiority Analysis of Ascending Colon Cleansing Using the Ottawa Scale; ITT and PP Analysis Sets (Applicant's Study Report)

Population	PREPOPIK N(%)	HalfLytely N(%)	Treatment D ifference: Prepopik-HalfLytely	1-Sided Lower bound 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
PREPOPIK Subjects 202-042 and 204-044 with unknown responder status were classified as treatment failures.
a. Excellent, good, or fair rating.

Source: Table9-3 of Sponsor's Study Report, Page 51 of 81

(b) (4)

Table 9: Responder Rate Comparisons between Overall and Ascending Colon in Study 01 and 02: ITT

	Overall Colon Aronchick Excellent + Good Responders	Ascending Colon Ottawa Excellent + Good + Fair Responders
	%	%
Study 01		
Prepopik Split Dose	84.2%	89.5%
Halflytely	74.9%	78.8%
Study 02		
Prepopik Day Before Dose	82.9%	81.3%
Halflytely	79.7%	84.0%

I concur with the reviewers and CDTL that the two major trials submitted in this NDA establish the efficacy of Prepopik and support its approval. I agree with the Clinical reviewers that from an efficacy standpoint the Split Dose regimen is the preferred regimen for approval. Trials reported in the published literature have demonstrated that split dose regimens provide superior bowel cleansing compared to regimens that are administered entirely on the day prior to colonoscopy. The 2008 American College of Gastroenterology guidelines for colorectal cancer screening recommend that colon cleansing regimens for colonoscopy be given in split doses and that this regimen be considered the standard of care.[1] The reason for this observation may be that the last dose in a split dose regimen is delivered more proximal to the actual procedure.

The team initially proposed only including the split dose regimen in the Dosage and Administration section of the product label, and I agreed with them. The applicant argued that there are reasonable circumstances in which it is not optimal for a patient to take a split dose regimen, e.g., patients who have a long distance to travel to endoscopy, and that it would be remiss to leave out those instructions from the product label, due to the needs of these patients. The applicant proposed alternative wording for the Dosage and Administration section of the label, which pointed to the split dose regimen as the preferred regimen. The team reviewed the proposal and found it acceptable, with revisions to the designation for the Day Before regimen to clarify that it is an alternative to the preferred split dose regimen for patients for whom the split dose regimen is inappropriate. I concur with these labeling recommendations, as the safety review of the Day Before regimen did not identify significant safety issues relative to the Split Dose regimen that alter the risk/benefit decision.

8. Safety

The integrated safety analysis of the two major phase 3 trials that support this NDA (Studies 01 and 02) included 601 patients exposed to Prepopik and 600 to HalfLytely. There were a number of relevant exclusion criteria in these trials, including renal insufficiency, uncontrolled hypertension, congestive heart failure, uncontrolled angina or myocardial infarction within the

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

prior 3 months, and active inflammatory bowel disease. In addition, because abdominal bloating, distension, pain/cramping, and watery diarrhea are known responses to colon cleansing preparations, they were not documented as adverse events unless medical intervention was required. The latter should be kept in mind when making comparisons to other colon cleansing preparations that did collect these as adverse events.

There were no deaths in the two trials. There were 3 serious adverse events (SAEs) in Study 01 (the Prepopik split dose trial), two on the HalfLytely arm and one on the Prepopik arm. There were 3 SAEs in Study 02 (Prepopik same day dose trial), two in the Prepopik arm and one in the Halflytely arm. The SAE in the Prepopik arm of Study 01 was acute pancreatitis. In Study 02, one of the patients in the Prepopik arm had an SAE of colon cancer, anastomotic complications from surgery and dehydration, and the other had acute coronary syndrome on study Day 13. None were considered treatment related.

The protocols included a plan to collect a baseline weight (only one assessment on study) and assessments of serum chemistry, PT/PTT, CBC/Diff, urinalysis, ECG, orthostatic vital signs (performed at baseline, day of colonoscopy, subsequent visit 24-48 hours after colonoscopy, a week after colonoscopy, and a month after colonoscopy). The serum chemistry included standard electrolytes, creatinine, total serum protein, albumin, total bilirubin, transaminases, alkaline phosphatase. The number of serial assessments in these two trials is unique for colon cleansing product registration trials (see Table 1 in Section 2 Background).

The Division of Biometrics VII (DB7) was consulted to assist in reviewing the safety dataset. They reviewed the safety data for cardiac arrhythmia, seizure and ischemic colitis. They also examined the laboratory data for changes from baseline, including mean changes and proportions of patients that shifted from normal baseline to abnormal. Summary tables of changes over time for each study are presented in the DB7 and CDTL reviews. The main focus of these analyses is to detect differential effects between the two arms, not the absolute effects occurring within each arm. Evaluation of intrapatient longitudinal changes can't be presumed from these data presentations. I will present some of the summary safety data from the clinical and DB7 reviews, as well as scatter plots provided to me upon request from the DB7 reviewer. These plots show individual outlier data and provide some information on extremes and the number of extreme values that occurred in the trials. In addition, longitudinal analyses of eGFR and creatinine were requested from the applicant. I will present some observations based on the data the applicant submitted in response to those requests.

Albumin, Total Bilirubin, Transaminases

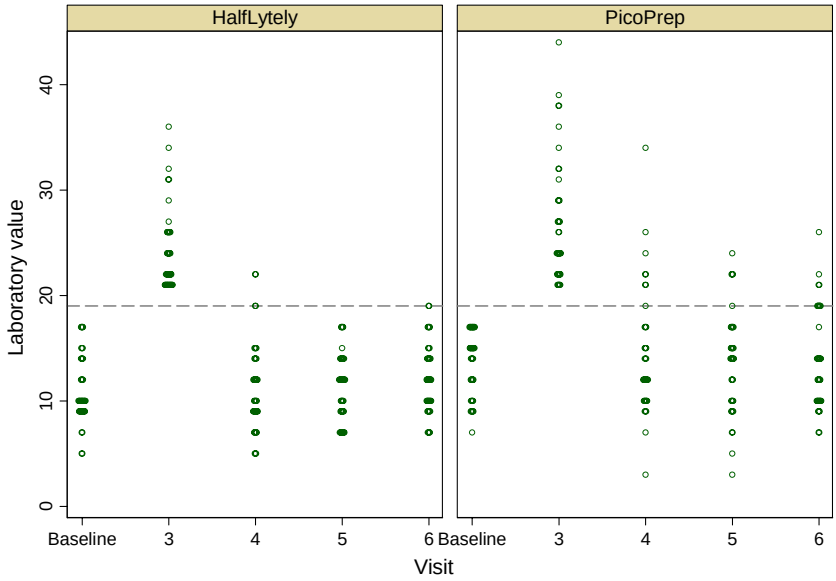
The major difference between the two study arms in liver effects was a higher proportion of patients in the Prepopik arm of Study 01 that developed an abnormal serum albumin level on the day of colonoscopy compared to the Halflytely arm (9.5% vs. 4.5%). In Study 02, a smaller number of patients in both arms developed abnormal serum albumin on the day of colonoscopy; however, the proportion remained approximately double on the Prepopik arm (5.8%) compared to the Halflytely arm (2.8%). Shift tables in the Clinical Review (Tables 35 and 36) indicate that the majority of the abnormal values were hyperalbuminemia. In Study 01, 8.8% Prepopik and 4.2% Halflytely arm patients had hyperalbuminemia. In Study 02, 5.8% Prepopik and 2.1% Halflytely arm patients had hyperalbuminemia. If the

hyperalbuminemia was due to dehydration, these data suggest that Prepopik was associated with a higher proportion of patients with dehydration and that dehydration was more common in the split dose regimen.

The liver function tables in the reviews also reveal that in both arms of both studies the mean bilirubin level nearly doubles from baseline on the day of colonoscopy, and then returns to baseline. In Study 01, 12.2% and 14% of the Prepopik and Halflytely patients shifted to an abnormal bilirubin on the day of colonoscopy, and in Study 02, 8% in each arm shifted to abnormal. The number of shifts dropped dramatically in the 24-48 hour follow-up assessment. There were also shifts to abnormal in transaminases observed in each study, but the proportions were smaller than the bilirubin increases. The group mean changes in the transaminase serum levels were correspondingly lower. The scatter plots for the patients that shifted to abnormal bilirubin levels were provided by the DB7 reviewer upon request and are presented below. The DB7 reviewer also provided a summary of the numbers and distribution of patients in each arm that developed transaminase levels ≥3 xULN and bilirubin levels ≥ 1.5 x ULN. He confirmed that Hy's law was not met in any of the patients.

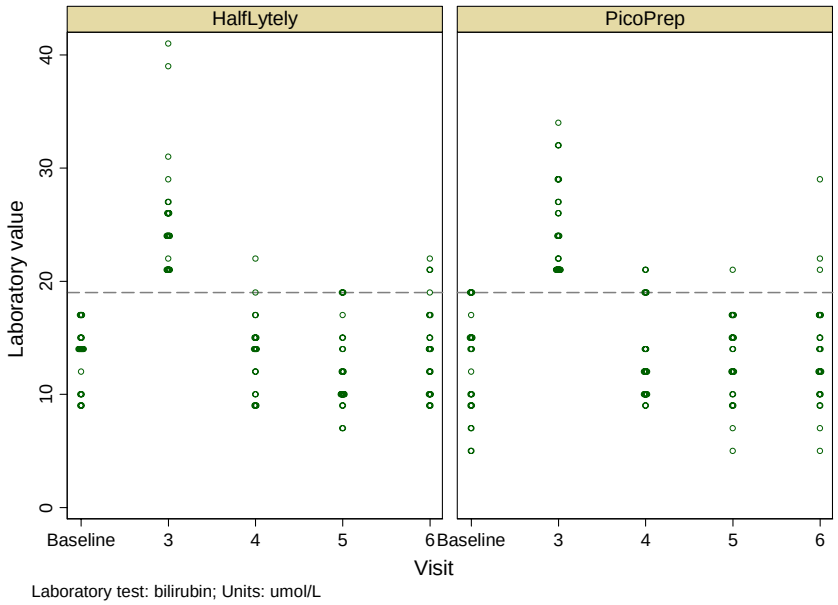
In the following plots, only the patients with normal baseline bilirubin values who shifted to abnormal on the day of colonoscopy are presented.

Figure 1: Study 01 Bilirubin Shifts in only patients who shifted to abnormal the day of colonoscopy



Laboratory test: bilirubin; Units: umol/L

Figure 2: Study 02 Bilirubin Shifts in only patients who shifted to abnormal on day of colonoscopy



Bilirubin elevations were also observed in the safety dataset submitted for the NDA for Suprep, which included two trials comparing Suprep to Moviprep. In the combined dataset, 9% of Suprep patients had a shift from normal bilirubin to high bilirubin, as did 13% of the Moviprep patients. Presumably the hyperbilirubinemia observed with colon cleansing regimens is related to fasting and/or dehydration. Patients with Gilbert syndrome can experience bilirubin elevations with dehydration.[2,3]

Serum Electrolytes

Similar analyses were presented for serum electrolytes/renal function (including eGFR).

Magnesium. A notable difference between Prepopik and Halflytely was the mean increase in serum magnesium in the Prepopik arm, which resolved by 24-48 hours post colonoscopy. The mean increase in the Prepopik arm is similar between the two studies, despite the more proximal dosing of the product in Study 02. The mean change was slightly less in the Day Before Prepopik regimen in Study 02: 0.18 mmol/L in Study 01 and 0.12 mmol/L in Study 02. In Study 01, 11.6% had serum magnesium levels that exceeded normal. The plots below show levels that exceeded the upper limit of normal were not markedly out of range. None were high at 24-48 hours post colonoscopy. In Study 02, 8.7% had serum magnesium levels that exceeded normal. One patient had a high magnesium at 24-48 hours post colonoscopy.

[2] Meyer BH, et al. Br J Clin Pharmac.;1995;39:169-171.
[3] Rodrigues C, et al. Am J Medical Sciences. E pub.

Figure 3: Study 01: Distribution of Magnesium Levels by Study Visit

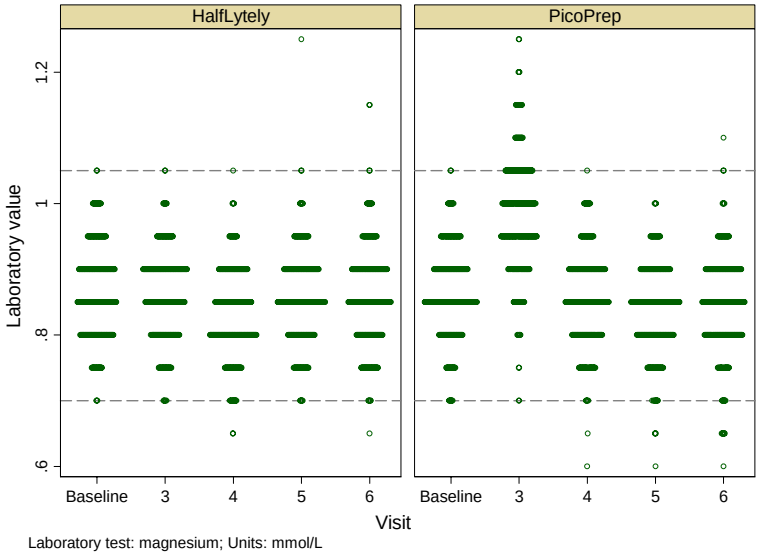
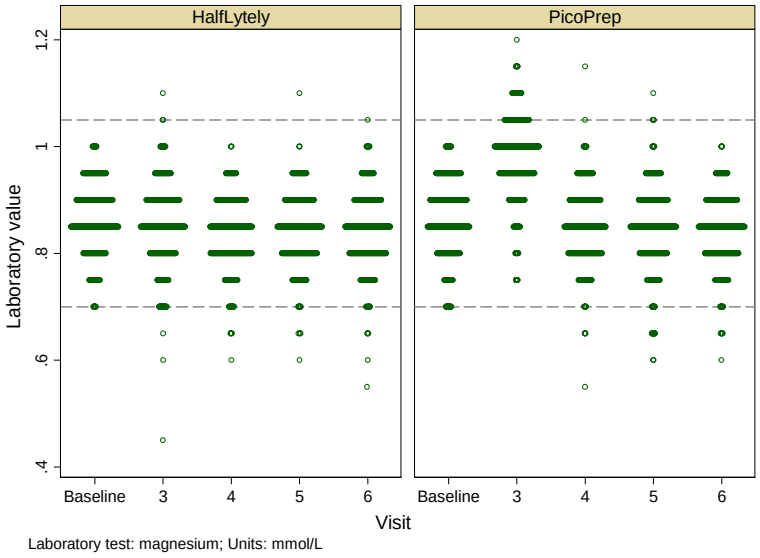


Figure 4: Study 02: Magnesium Levels Across Study Visits



The Canadian product label carries a contraindication for use in patients with severe renal insufficiency due to the potential for accumulation of magnesium. The Clinical reviewers consulted with nephrologists within the division (Division of Gastroenterology and Inborn Errors Products) regarding this issue and ultimately recommended that the US product label should also carry this contraindication. The applicant proposed instead that this should be limited to a Warning, pointing out that Suprep, an approved osmotic colon cleansing product, also contains magnesium and does not have a contraindication. The reviewers considered the applicant's position; however, they noted that Suprep contains much less elemental magnesium in the form of magnesium sulfate (b) (4) compared to Prepopik (b) (4) in which the magnesium is in the form of magnesium citrate. The reviewers pointed to the evidence that the magnesium in Prepopik is bioavailable, more so than in Suprep. I concur with the

recommendation for a contraindication, as some patients with severe renal insufficiency may have a higher baseline serum magnesium than patients without renal insufficiency.

Hypokalemia A higher proportion of patients in the Prepopik arm of Study 01 shifted to abnormal potassium levels on the day of colonoscopy than on the HalfLytely arm, 10% vs.6%; however, the proportion of patients shifting to abnormal was similar between arms in Study 02 (5%). The mean change in each arm in Study 01 was a decrease of approximately 0.1 mmol/L. In Study 02, there was a mean decrease of 0.06 mmol/L in the Halflytely arm, but in the Prepopik arm the mean change was an increase of 0.02 mmol/L. The Clinical review contains shift tables that delineate what proportion of patients shifted to high vs. low values (Table 35 and Table 36). The majority of shifts were to hypokalemia. In Study 01, 7.3% Prepopik and 4.1% Halflytely patients were hypokalemic on the day of colonoscopy. In Study 02, 4.7% Prepopik and 4.8% Halflytely patients were hypokalemic on the day of colonoscopy.

Chloride. The products differed in impact on serum chloride. In both trials , the mean serum chloride dropped in the Prepopik arm on the day of colonoscopy. The mean decrease was 1.8 mmol/L in Study 01 (more proximal dosing) and 0.9 mmol/L in Study 02. In Study 01, 3.7% of the patients treated with Prepopik had hypochloremia on the day of colonoscopy. In Study 02 a lower proportion of patients, 1.0%, developed an abnormal serum chloride.. The apparent difference between trials in the changes in chloride associated with Prepopik could be related to differences in the proximity of last dose of Prepopik relative to the blood draw in the two studies (more proximal in Study 01). In contrast, 1% of Halflytely arm patients in Study 01 and none of the HalfLtyely arm in Study 02 developed an abnormal serum chloride. All abnormal chloride values were low values.

Hyponatremia. The proportion with hyponatremia in the Prepopik arm was higher on the day of colonoscopy in Study 01 in the Prepopik arm, 3.7% vs. 1%. This difference could be related to the proximity of dosing of Prepopik in Study 01, as the proportion of hyponatremia was the same in the two arms in Study 02 (1.0%), in which both products were administered completely the day prior to colonoscopy). This pattern was also observed for hypokalemia.

The DB7 reviewer noted that in Study 01 "there was a significantly greater decrease in mean sodium levels from baseline [DMC=-0.6 mmol/L; (95% CI=-0.9, -0.2)] in the Prepopik arm." The mean change in the Prepopik arm was a 0.7 mmol/L decrease vs. a 0.1 mmol/L decrease on the Halflytely arm. In Study 02, the mean change was a 0.2 mmol/L increase in the Prepopik arm and a 0.5 mmol/L increase in the Halflytely arm. There was one extreme value, a patient with a sodium of 121 mmol/L on the day of colonoscopy. The patient was a 70 year old woman who had nausea and vomiting on the day of colonoscopy and required intravenous ondansetron. She was also hypochloremic (chloride=81 mmol/L) and the Clinical reviewers considered the vomiting to be a contributing factor to the electrolyte changes.

Both sodium and chloride changes observed with Prepopik in these trials seemed to be related to the dosing regimen and proximity of the last dose in the split dose regimen studied in Study 01. The changes observed in each arm in each study are summarized in the table below.

Table 10: Proportion of Shifts from normal baseline to low values on day of colonoscopy

	Study 01			Study 02	
	Prepopik	Halflytely		Prepopik	Halflytely
	% shift to Low	% shift to low		% shift to low	% shift to low
Potassium	7%	4%		5%	5%
Sodium	4%	1%		1%	1%
Chloride	4%	0.3%		1%	0%

Sodium picosulfate/magnesium citrate has been marketed outside the US for years. The post marketing safety events related to hyponatremia were explored in light of the approximate 28 million uses up to December 2011. The Clinical reviewer summarized the periodic safety update reports for postmarketing safety data over the time since its approval outside the US, which were submitted to this NDA. In addition, the OSE Division of Pharrmacovigilance-1 reviewers conducted an AERS search for "electrolyte imbalance" (including sodium, potassium, chloride, magnesium, calcium, phosphorus and bicarbonate, as well as dehydration) from January 1980 to March 2012. Table 4 of their review includes 3 reports (all from outside the US) for "sodium picosulfate with magnesium oxide and citric acid" used as a bowel preparation. All were cases of hyponatremia. Two had associated hypokalemia, and one of those also had hypocalcemia. One case ended in death (aspiration pneumonia). One suffered a grand mal seizure and one patient went into a coma. These patients were on medications that could have contributed to the event. One was hyponatremic prior to taking the product.

Clinical manifestations of hyponatremia include mental status changes, cerebral edema and seizures. The Clinical Reviewer's tabulation of the applicant's summary post marketing safety reports indicates the product has been associated with serious CNS adverse reactions, which she attributed to hyponatremia (hyponatremia and dehydration for seizures). The tables in Section 7.7 of her review include 5 patients with seizures: 2 in children (one 5 yo and one 12 yo)., 2 in patients over the age of 60 years (74 yo and 63 yo), and 1 in a 39 yo. In addition there was one cerebral edema (78 yo), one coma (55 yo), and one case of delirium (55 yo). Hyponatremia is a known potential complication of bowel cleansing regimens. Elderly patients and patients with pre-existing conditions or concomitant medications that predispose to hyponatremia are at particular risk for severe hyponatremia and serious neurological sequelae. The approved preparations carry warnings about these serious safety issues. In the context of the 28 million uses outside the US, these postmarketing reports aren't inconsistent with what would be expected for a colon cleansing product.

Creatinine and eGFR

Interestingly, there was a slight and consistent upward trend over time, through the last study visit (one month post colonoscopy), in both creatinine and EGFR in both study arms of both trials. (See summary table next page.) Examination of shifts to a high creatinine in the Clinical review Table 35 for Study 01 revealed that on the day of colonoscopy, there was a numerically higher percentage of patients in the Halflytely arm with a shift to abnormal creatinine – 4.9% vs. 1.9% on the Prepopik arm. In Study 02, where both products were administered the day prior to colonoscopy, the proportion of high creatinines was similar between arms, and was comparable to that observed in the Halflytely arm of Study 01 – 5.9%

Halflytely vs. 4.5% Prepopik. This pattern might reflect differential hydration status. The final dose of Prepopik in Study 01 was taken on the day of the colonoscopy and involved consumption of 870 cc of water. However, the relative proportion of hyperalbuminemia (which might reflect dehydration) in Study 01, which occurred in twice as many patients on the Prepopik arm than on the Halflytely arm (8.8% vs. 4.2%), does not correlate with the pattern of high creatinine. In Study 02, hyperalbuminemia was also observed in nearly twice as many Prepopik treated patients than Halflytely treated patients.

Despite the higher proportion of shifts to high creatinine on the day of colonoscopy in the Halflytely arms, there was a numerically higher proportion of patients in the Prepopik groups of both trials that shifted to a low eGFR than Halflytely. It is notable that at 24-48 hours post colonoscopy, there was an increase in proportion of patients with high creatinine on the Prepopik arm of both trials: from 1.9% on the day of colonoscopy to 6.8% in Study 01 and from 4.5% on the day of colonoscopy to 7.2% in Study 02. In contrast, for Halflytely, the proportion with high creatinine dropped slightly to 4.1% from 4.9% in Study 01, and was relatively stable in Study 02. By one week post colonoscopy, in Study 01, 3.8% Prepopik and 4.9% Halflytely treated patients had a high creatinine. In Study 02, 3.8% of patients in both arms had a high creatinine. The data at 1 month appear consistent with the one week post colonoscopy data, with the exception of an increase in patients with high creatinine and low eGFR in the Prepopik arm of Study 02, and a slight increase in the proportion of patients with low eGFR in both arms of Study 01. See summary table below.

Table 11. Summary of Proportion of Patients with Normal Baseline with Shift to Abnormal Values of Creatinine or eGFR at Study Assessment Points; By Study and By Treatment Arm

	Study 1 (SPLIT Dose PREPOPIK)				Study 2 (Dose Day Before Colonoscopy)			
	Prepopik		Halflytely		Prepopik		Halflytely	
	% patients		% patients		% patients		% patients	
	High Creatinine	Low eGFR	High Creatinine	Low eGFR	High Creatinine	Low eGFR	High Creatinine	Low eGFR
Day of Colonoscopy	2	10	5	8	5	13	6	11
24-48 h post	7	14	4	10	7	13	6	12
1 week post	4	10	5	8	4	6	4	13
1 month post	4	11	5	10	7	11	4	11

These data can be contrasted to what was observed in the Suprep NDA, in which Suprep (sulfate ionic solution) was compared to the PEG plus electrolytes product Moviprep. The shifts to high creatinine from normal on the day of colonoscopy in that NDA are summarized in the table below:

Table 12: Summary of shifts from normal baseline creatinine to abnormal on the day of colonoscopy in NDA 22372 for Suprep

	Study 301 (Same day dosing)		Study 302 (Split dosing)	
	Suprep	PEG+E	SUPREP	PEG+E
Proportion of patients with shift from normal baseline creatinine to abnormal on the day of colonoscopy	3%	2%	2%	0.1%

The proportion of shifts to high creatinine in Study 01 and Study 02 in the Prepopik NDA are numerically higher than observed in the major trials that supported the Suprep NDA; however, cross study comparisons are exploratory in nature only. There are multiple factors that could be responsible for the relative small numeric differences between these two applications. These data from the two different colon cleansing preparations administered in the trials submitted in the Suprep NDA show that the observations in Study 01 and Study 02 in this application are not unique on the day of colonoscopy.

The CDTL review presented a summary of mean change in creatinine at different time points across the two trials in his review. The following table, reproduced from that review, provides the number of patients the CDTL identified in the combined data from the two trials with a shift to abnormal on Visit 3 (day of colonoscopy): 17 on Prepopik arms and 29 on Halflytely arms. He summarized the mean change in creatinine in this group, compared to those patients who did not shift to abnormal on that day. He concluded the shifts were most likely related to dehydration. Although the number of patients with shifts to abnormal in the Prepopik treated group was lower than the Halflytely group, the incremental mean increase was numerically higher with Prepopik. In addition, as noted above, the proportion of patients with a shift to high increased further on the 24-48 hour post visit in the Prepopik treated patients, not the Halflytely patients, and there was a higher number of patients in the Prepopik arms that shifted to a low eGFR on the day of colonoscopy than in the Halflytely arms. Therefore, this analysis does not completely describe what was happening with those patients.

Table 13. Mean increase in creatinine at Visit 3 in subjects with normal baseline creatinine

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**
Prepopik		17	**0.19**
HalfLytely	Normal at baseline to Normal	505	0.02
Prepopik		505	0.02

Visit 3 = Day of colonoscopy

The following table summarizes the mean change in eGFR observed in these two trials.

Table 14: Mean change in eGFR from baseline to day of colonoscopy by trial and arm.

	Study 01		Study 02	
	Prepopik	Halflytely	Prepopik	Halflytely
Change in mean eGFR	-3.4	-3.9	-4.8	-3.8

The CDTL also presented group mean analyses for patients whose creatinine and eGFR were normal on the day of colonoscopy, but who had an abnormal creatinine on the final visit, Day 30. He noted that even though in the major incremental change in creatinine occurred between the one week post colonoscopy visit and the final visit on Day 30, there was evidence of a progressive decline in mean eGFR over each assessment point during the month of follow up. This is shown in the two tables that follow, which are reproduced from the CDTL review. The group mean changes are more striking in the Prepopik treated patients than in the Halflytely patients. The CDTL examined the individual data for each of these subjects and noted that this trend was not as obvious at the individual level. In addition, he couldn't identify an adverse event pattern associated with these changes. He concluded that the clinical significance of these changes is unknown. There were patients with creatinine elevations on Day 30 who had experienced creatinine elevation on the day of colonoscopy (Visit 3).

Table 15. Creatinine Values 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
Prepopik	22	0.02	0.05	0.06	0.24

Table 16. eGFR [estimated glomerular filtration rate (mmol/L)] across study days for subjects with Normal Creatinine Visit 3 (Colonoscopy) and Abnormal High Creatinine 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
Prepopik	22	-4.6	-6.2	-12.2	-29.8

Because these analyses cannot identify whether there were meaningful longitudinal deterioration in eGFR and creatinine in individual patients, the applicant was asked to present longitudinal data for patients who had experienced deterioration of eGFR and creatinine on study. In order to identify characteristics that increase risk of deterioration, the applicant was also asked, in those patients who had developed these changes, to provide the patients' ages, whether they had experienced orthostatic changes, and their concomitant medications. The applicant submitted the serial creatinine and eGFR line listings for each patient, along with demographic information; however, concomitant medications and serial orthostatic pulse and BP data were presented in separate sets of line listings.

The line listings were reviewed and four categories of creatinine or eGFR changes were identified for patients who had normal creatinine and/or eGFR at baseline. Each category (each mutually exclusive) and the number of patients in each category is summarized in the table below.

Table 17: Subsets of Patients with Evidence of Shifts from Normal Baseline Creatinine and/or eGFR by Study and Treatment Arm

	Study 01		Study 02	
	Prepopik	Halflytely	Prepopik	Halflytely
	N/305	N/ 298	N/296	n/302
Developed High Creatinine before Day 30 and sustained it at Day 30	4 (1%)	7 (2%)	7 (2%)	6 (2%)
High Creatinine Day 30 with Evidence of increasing creatinine Prior	4 (1%)	4 (1%)	7 (2%)	2 (1%)
Total	8 (3%)	11 (4%)	14 (5%)	8 (3%)
High Creatinine followed by improvement to normal range, but without return to baseline by Day 30	7 (2%)	7 (2%)	14 (5%)	8 (2%)
eGFR drops to low and remains low at Day 30 AND creatinine deteriorates over the same time without reaching abnormal	13 (4%)	14 (5%)	8 (3%)	16 (5%)

If the first two categories are totaled (patients with high creatinine on Day 30 who had evidence of deterioration of renal function through either high creatinines or deteriorating creatinine, the treatment arms are similar, with percentages running 3-5%. The category of eGFR sustained abnormal with associated deterioration in creatinine (without reaching high) was also similar across arms, ranging 3-5%. This suggests bowel cleansing with either of the products is associated with some evidence of renal deterioration that has not completely reversed by one month in approximately 6-10% of patients, depending upon how loosely "deterioration" is defined.

The ability to analyze the data for impact of concomitant medication and orthostatic changes was limited by the presentation of the data. High level review of the line listings revealed that some of the events were associated with documented orthostatic changes, but not all. In many patients the orthostatic changes were not documented on the day of colonoscopy, but were delayed at 24-48 hours, and even at 1 week in some patients. Many patients were on concomitant antihypertensives (including ARBs) and/or NSAIDs; however, many were not. A summary listing of the patients in the two major categories, with their creatinine shifts (baseline and Day 30 value) and concomitant medications are provided below for context. The concomitant medications include medications administered at colonoscopy. Medications that are listed following the colonoscopy sedation agents are those that were started subsequent to the colonoscopy. I have marked in italics those patients who had abnormal baseline eGFR despite a normal creatinine. In addition, I have marked with underlining patients who had obvious intervening health issues that should be considered in interpreting the meaningfulness

of high creatinines subsequent to colonoscopy. Clearly there are some patients with documented alternative reasons for having elevated creatinine at Day 30. In addition, there is a substantial subset with an intervening creatinine before a high Day 30 value that had a documented drop in creatinine down to a value that was normal or upper limit of normal. This raises questions about the meaningfulness of the Day 30 changes. The visit numbers correspond to the following days in the study: Visit 3= colonoscopy, Visit 4=24-48h post colonoscopy; Visit 5 = 1 week post, Visit 6 = 1 month post.

SUBGROUP: High creatinine sustained to end

Prepopik (N=11)

104-052 (High on Visits 3,4,5,6) creatinines: 79, 91
Medications: amlodipine, hydrochlorothiazide (hctz), prn NSAID over the counter, fentanyl/midazolam

107-021 (High on Visits 3, 4, 5, 6) creatinines: 83, 103
low eGFR at baseline
Clonidine, hctz, lovastatin, metformin, trazodone, fluoxetine, montelukast, topical metronidazole, propofol, lidocaine; ciprofloxacin for uti 21d post colo.

107-025 (High on Visits 4, 6) creatinines: 84, 88
low eGFR at baseline
Asa, clonidine, metoprolol, potassium, caduet, levothyroxine, omeprazole, propofol, lidocaine.

107-053 (High on Visits 4, 6) creatinines: 91, 127
Simvistatin, propofol, lidocaine.

202-023 (High on Visits 3,5,6) creatinines: 71, 115
Amlodipine, hctz, lisinopril, loratidine; propofol, midazolam, ketamine.

204-026 (High on Visits 3,4,5,6) creatinines: 81, 86
low eGFR at baseline
Olmesartan; fentanyl, lidocaine, midazolam, pethidine, propofol

209-021 (High on Visits 5,6) creatinines: 99, 105
Fiorecet, olmesartan, metoprolol, metformin, sildenafil; propofol

209-038 (High on Visits 4,5,6) creatinines: 103,109
low eGFR at baseline
Aliskiren, colesevelam, irbesartan, Advair; propofol

212-041 (High on Visits 4,6) creatinines: 103, 112
low eGFR at baseline
Aspirin, valsartan, colchicine, glipizide, ibuprofen prn; propofol, meperidine

212-043 (High on Visits 3, 4, 6) creatinines: 74, 88

low eGFR at baseline
Aspirin, valsartan, hctz, metformin, amaryl, tramadol, rabeprazole, xanax,; meperidine, propofol. Cardiac Cath 14 days post colonoscopy; MI. carvedilol, prasugrel, valsartan, simvastatin.

212-080 (High on Visits 3, 6) creatinines: 97, 106
low eGFR at baseline
Ibuprofen prn; meperidine, propofol

Halflytely (N=13)
101-048 (High on Visits 3,4,5,6) creatinines: 103, 133
low eGFR at baseline
Amlodipine, hctz, lisinopril; propofol, midazolam, ketamine.

103-038 (High on Visits 3,4,5,6) creatinines: 80, 87
low eGFR at baseline (however, there is a f/u normal creatinine value after Day 30)
fentanyl, midazolam, diazepam

104-019 (High on Visits 4,6) 101, 114
Fentanyl, midazolam

104-038 (High on Visits 4, ?,6) missing Visit 5 data creatinines: 79,88
Ibuprofen prn, fluticasone, ipratropium, ramipril, rosuvastatin, albuterol, salbutamol, Advair, tiotropium, Vicodin; fentanyl, midazolam

105-021 (High on Visits 3, 5,6) creatinines: 74, 85
low eGFR at baseline
Bupropion, eszopicione, meloxicam, omeprazole, pantoprazole; propofol

106-029 (High on Visits 3,6) creatinines: 79, 85
low eGFR at baseline
Alendronate, methotrexate; meperidine, propofol

107-093(High on Visits 3,4,5,6) creatinines: 84, 90
low eGFR at baseline
Irbesartan; lidocaine, propofol

202-030 (High on Visits 3,5,6) creatinines: 95, 115
low eGFR at baseline
Irbesartan, Asa, clopidogrel, rosuvastatin, testosterone; propofol

207-044 (High on Visits 3,4,6) creatinines: 82, 95
low eGFR at baseline
Escitalopram, estrogen, naproxen prn, topiramate; fentanyl, lidocaine, midazolam, propofol; Librax started 1 week after colonoscopy; ibuprofen bid started 3 weeks post colonoscopy.

209-009 (High on Visits 3 ,4,6) creatinines: 101, 112
Asa, rosuvastatin, carvedilol, furosemide, amlodipine/benazepril, dofetilide, clopidogrel, warfarin; propofol, fentanyl

209-025 (High on Visits 4,5,6) creatinines: 84, 95
low eGFR at baseline
Valsartan, alendronate, atorvastatin, glyburide, metformin, pioglitazone; fentanyl, propofol

211-010 (High on Visits 5,6) creatinines: 77, 105
Amlodipine/benazepril, nabumetone, micaris/hctz, valsartan, zolpidem, clonidine, colchicine; propofol, lidocaine; darifenacin, lortab, allopurinol.

212-005 (High on Visits 3,4,6) creatinines: 102, 114
low eGFR at baseline
Losartan, asa, calcium, cetirizine, esomeprazole, ezetimibe, finasteride, glucosamine, levothyroxine, metoprolol, pravastatin; propofol (1 week PRIOR to colonoscopy, administered for EGD) meperidine, propofol

High creatinine Day 30 with evidence of Deterioration Prior

Prepopik (N=11)

104-017 62, 88
Sertraline, simvastatin, spironolactone; fentanyl, midazolam; ibandronate started 6 days post colonoscopy.

104-044 90, 111
Nasonex,; fentanyl, midazolam

108-05 74.87
low baseline eGFR
Esomeprazole, fluoxetine, lorazepam, Prempro; fentanyl, midazolam, benadryl

109-22 57, 87
labetalol, ventolin, clobetasol, Embrel, domeboro, propofol

202-54 76, 85
low baseline eGFR
Simvastatin, levothyroxine; propofol; ibuprofen started for dental implant 4 weeks after colonoscopy.

204-028 86, 145
Alprazolam, citalopram, hydrocodone, indomethacin, levothyroxine, lisinopril, omeprazole, simvastatin; fentanyl, midazolam, Demerol.

204-042 73, 88
Prednisone, risedronate, cetirizine; fentanyl, lidocaine, midazolam, Demerol, propofol

208-13 59, 109
low baseline eGFR
Asa, lovastatin, timolol, latanoprost; propofol, O2, D5NS 500cc.

209-026 79. 108
Fentanyl, propofol; lisinopril/hctz

210-21 69, 88
low baseline eGFR
Lisinopril; propofol, lidocaine

211-024 90, 105
Pravastatin, meloxicam, citalopram, lisinopril, labetalol, zolpidem; propofol, methodone, lidocaine

Halflytely (N=6)
103-024 71, 93
omeprazole, oxybutynin, erythromycin for cystitis prophylaxis, lisinopril; fentanyl, midazolam; ciprofloxacin x 7 days for UTI started 2 weeks post colonoscopy.

103-043 92, 105
ACE inhibitor, propanolol, rabeprazole; fentanyl, midazolam; Proctofoam, levofloxacin x 7 days started 5 days post colo for URI

103-057 57. 96
Asa, calcium, insulin, simvastatin, valsartan; fentanyl, midazolam; ciprofloxacin x 10 days started 3 days after colonoscopy for uti; ampicillin x 4 days started 25 days post colonoscopy

106-007 84, 104
Fenofibrate, testosterone, fluticasone, cefuroxime x 5 days ended 11 days prior to colonoscopy; propofol, meperidine

201-032 98, 109
Rosuvastatin; propofol, lidocaine; corticosteroid hemorrhoid cream

209-24 83, 87
low baseline eGFR.
Amlodipine, fosinopril, asa, naproxen BID; fentanyl, propofol

For comparison, the major clinical trials submitted in support of the Suprep NDA included creatinine assessments at baseline, day of colonoscopy and at one month. The following table summarizes the proportions of patients who had shifted to abnormal on the day of colonoscopy

(Visit 2), at one month only (Visit 3) , and on both the day of colonoscopy and 1 month. The methods for deriving the data in this table aren't the same as Table 17 above. For example, unlike the Suprep/Moviprep table, the subgroups enumerated above do not comprehensively reflect all patients with an elevated creatinine at 1 month since patients who had a solitary elevation at Day 30 without evidence of intervening deterioration were not included. In addition, as noted earlier in this review, there were patients in the Prepopik NDA whose creatinine did not shift to abnormal until the 24-48 hour post colonoscopy time point or at 1 week . Those assessment times were not included in the Suprep NDA trials. As summarized earlier, on the day of colonoscopy (Visit 3), 1.9% Prepopik and 4.9% Halflytely treated patients in Study 01 and 4.5% and 5.9%, respectively, in Study 02 had creatinine elevated to abnormal. These percentages are consistent with the percentages in the last row of the Suprep/Moviprep table below, although the split dose regimens in the Suprep NDA had numerically lower rates on the morning of colonoscopy than the split dose Prepopik regimen in Study 01. These cross study comparisons are exploratory in nature and the numeric differences cannot be judged to represent meaningful differences.

Table 18: New High Creatinine By Study and By Study Visit

Day of New High Creatinine	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
Visit 2 Only Colonoscopy	6 (3%)	4 (2%)	4 (2%)	1 (0.6%)
Visit 3 Only One month	7 (3.6%)	7 (3.6%)	5 (2.8%)	7 (3.8%)
Visit 2 and 3 Colonoscopy and One month	2 (1%)	1 (0.5%)	0	1 (0.6%)
Visit 2 all Colonoscopy	8 (4%)	5 (3%)	4 (2%)	2 (1%)

Subset Analyses of the Patients with High Baseline Creatinine:

Some patients enrolled in Studies 01 and 02 had abnormal baseline creatinines. The DB7 reviewer identified 40 Prepopik and 28 Halflytely arm patients in Study 01 that had an abnormal creatinine at baseline (approximately 9%). An even higher number, 79 and 84, respectively, had low eGFRs. In Study 02, 24 Prepopik and 27 Halflytely arm patients had abnormal creatinine levels at baseline (13% and 9%), and 92 and 73 had low eGFRs.

Review of individual patient data revealed the vast majority had stable or improved creatinine by Day 30. Exceptions were 3 patients with worsened creatinine at Day 30, in whom the degree of worsening was not substantive. One, on the Halflytely arm of Study 01, had an additional follow up creatinine evaluation after Day 30 that returned to baseline. Another on the Halflytely arm of Study 01 shifted from a baseline creatinine of 85mmol/L to 89 mmol/L at Day 30. A Prepopik arm patient in Study 02 increased from a baseline creatinine of 108 mmol/l to 111 mmol/L.

The following table summarizes the data for the patients with abnormal baseline creatinine in the major trials that supported the Suprep NDA. Similar to the Study 01 and Study 02, the Suprep/Moviprep trials included approximately 10% of patients with abnormal baseline creatinine. The proportion with deterioration to higher creatinine on study was similar to the proportion of patients who shifted from normal at baseline to abnormal in the same trials. There were numerically more patients with baseline high creatinine that shifted higher at the 1 month follow-up in the Suprep NDA trials than in Study 01 and Study 02 in the current NDA.

Table 19: Shifts in Creatinine in Patients Whose Baseline Creatinine Was High

	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
Proportion with **High Baseline Creatinine** [Range]	20 (10.3%) [1.2-1.6]	5 (11.9%) [1.2-2.1]	14 (7.7%) [1.3-1.6]	15 (8.2%) [1.2-2.8]
Creatinine Increased Further at Visit 2 Only [Range]	2 (1.0%) [1.4-1.5]	0	2 (1.1%) [1.4-1.5]	0
Creatinine Increased Further at Visit 3 Only [Range]	1 (0.5%) [1.4]	4 (2.1%) [1.3-1.6]	1 (0.6%) [1.7]	3 (1.6%) [1.6-2.3]
Creatinine Increased Further at Visit 2 AND Visit 3 [Range]	1 (0.5%) [1.4]	4 (2.1%) [1.3-2.0]	1 (0.6%) [1.4]	0
Total with Creatinine Increased Further at Visit 3	2	8	2	3

Serial Serum Chemistry Changes in the Context of Other NDA Datasets:
The trials submitted in this NDA are unusual for bowel cleansing product registration trials in that they incorporated multiple assessments after the day of colonoscopy. In my review of the Suprep NDA, I examined the reviews of previously approved osmotic bowel prep products and summarized the extent of follow-up evaluations in the trials supporting those applications. The following is reproduced in part from my Suprep NDA review. All comparisons to Prepopik are exploratory cross study comparison.

Moviprep NDA: Electrolytes were evaluated <u>on the day of colonoscopy</u> in two Moviprep registration trials. The labeled electrolyte data were limited to the same day regimen (Moviprep vs. OSP); however, the NDA clinical review included the following summary:

Table 20: Summary of Changes in Electrolytes Observed in Moviprep Trials

	German Study (Split Dose)		French (Same Day Regimen)	
	Moviprep %	GoLytely %	Moviprep %	OSP %
Sodium				

	German Study (Split Dose)		French (Same Day Regimen)	
Hypernatremia	1%	1%	2%	5%
Hyponatremia	2%	2%	0	2%
Potassium				
Hyperkalemia	0	0	1%	1%
Hypokalemia	5%	8%	8%	31%
Creatinine Increased	2%	1%	1%	2%
BUN Increased	0	0	1%	2%
Increased AST/ALT	7%/3%	5%/3%	NA	NA

The most common electrolyte abnormality (aside from hyperphosphatemia) was hypokalemia. Creatinine increases were observed in the range of 1-2%, similar to the Prepopik split dose arm on the day of colonoscopy. The rate of hypokalemia was similar to the rate observed for Prepopik. The rate of hyponatremia is numerically lower than that observed for Prepopik.

Visicol NDA (2-3 day post colonoscopy follow-up): The Visicol NDA (21-097, approved in 2000) included a Day 2-3 post colonoscopy evaluation. The comparator product was a PEG based product (Nulytely) administered in a split dose regimen. It was the only NDA identified with a post colonoscopy assessment other than the Suprep NDA.

The summary of group mean electrolyte changes, reproduced below from the NDA review, shows that the day of colonoscopy (Visit 1) changes had resolved or nearly resolved by Day 2-3 (Visit 2). Exploratory cross study comparisons of the mean changes observed for sodium and potassium in these trials vs. the Prepopik trials revealed that on the day of colonoscopy Prepopik was associated with a mean decrease in sodium of -0.7 mmol in the split dose trial, compared to a mean increase in sodium in both Nulytely and Visicol. At the 2-3 day follow up, a residual mean increase remained for Visicol, whereas the change had resolved in the Nulytely arm. For Prepopik split dose regimen, at the 1-2 day follow up, a 0.3 mmol decrease remained. For potassium, in both Visicol and Nultytely there was a mean reduction in potassium at both the day of colonoscopy and the 2-3 day follow-up. For the Prepopik split dose regimen, there was a mean reduction in potassium on both the day of colonoscopy and the 1-2 day follow up similar in magnitude to that observed with Nulytely.

Table 21: Mean Changes in Electrolytes (including 1-2 Days post Colonoscopy Visit 2) in the Visicol NDA

Table 26. Mean Changes in Electrolyte Values from Baseline - Combined Data Studies 301 and 302

	Diacol (n=427)			NuLYTELY (n=432)		
Analyte (normal range)	Screening	Visit 1	Visit 2	Screening	Visit 1	Visit 2
Sodium (138-148 mEq/L)	138.4	2.3	0.3	138.3	0.7	0.0
Potassium (3.5-5.1 mEq/L)	4.2	-0.6	-0.1	4.2	-0.1	-0.1
Calcium (8.6-10.4 mg/dL)	9.1	-0.5	-0.1	9.1	-0.1	-0.1
Phosphorus (2.4-4.7 mg/dL)	3.3	3.7	-0.7	3.3	0.0	0.0
Bicarbonate (22-30 mEq/L)	27.3	-1.7	-0.5	27.1	-0.9	-0.4
Magnesium (1.3-2.5 mg/dL)	1.9	0.0	0.0	1.9	0.0	-0.1

Source: ISS Table 26

The summary table of treatment emergent chemistry adverse events from the Visicol NDA clinical review is reproduced below. Unfortunately, this table doesn't discern between events documented on the day of colonoscopy and those 2-3 days later. Elevated creatinine was reported in 1.2% of Visicol patients vs. 2.5% in the NuLytely control arm, which is similar to what was observed on the day of colonoscopy for split dose Prepopik (2%). However, the rates of shift were numerically higher on the 24- 48 hour follow up for patients treated with Prepopik in both the split dose and day before regimens. Again these are exploratory comparisons cross study comparison, and one cannot conclude that any apparent differences are in fact real differences.

Summary [electrolyte shifts]: The trials submitted to support this NDA documented fluid and electrolyte shifts that are known to be associated with colon cleansing products. Class labeling has been developed to address these known adverse reactions and the Prepopik label should also carry these warnings. As noted earlier, this NDA is unusual because the trials incorporated more follow up assessments than previous NDAs. These additional assessments demonstrated recovery of electrolyte changes, generally by the 24-48 hour post colonoscopy assessment. However, there was a subset of patients who had elevation creatinine at 24-48 hours and one week post procedure, and a few persisted out to one month. Orthostatic changes

were documented at 24-48 hours and even at 1 week. The presumed etiology of the creatinine and eGFR changes is volume contraction, perhaps compounded by resuming hypertension medications and/or other medications such as NSAIDs. The contribution of the effects of sedation during colonoscopy can't be excluded.

Bowel cleansing products are designed to cause diarrhea. They can cause vomiting and volume contraction. A thorough knowledge of each patient's physiological response to a bowel prep could be expected to reveal a variable impact, depending on whether a patient becomes nauseated, vomits, cannot or does not adequately hydrate, has co-existing medical conditions that cause altered renal perfusion or renal function, or takes medications that alter renal perfusion/renal function. There are multiple factors that could influence how an individual patient responds to osmotic catharsis. Sedation for colonoscopy may also cause hypotension, which could negatively impact renal function.

The submitted dataset shows a range of serum chemistry responses to Prepopik. Obtaining additional information for further analysis may help identify those patients who are more at risk for having adverse effects associated with colon cleansing with Prepopik, including renal effects. Such information may help identify ways to more effectively provide supportive care during and after bowel preps. The reviewers discussed the data in the current NDA and concurred that the class labeling for osmotic bowel cleansing products could be further strengthened. They recommended cautionary wording regarding volume replacement in patients with congestive heart failure, and the addition of checking for signs of orthostatic changes when assessing for dehydration. The reviewers recommended adding the clinical trial data on the proportion of patients who developed orthostatic changes, and the timing of development of orthostatic changes. They recommended moving the seizure warning up to the second warning, and moving the use in renal impairment warning up to the third warning in the list in Section 5 WARNINGS and PRECAUTIONS. They recommended adding the statement "These patients may be at increased risk for renal injury" and the contraindication information referring to magnesium in this section as well.

In addition, the reviewers recommended a PMR study as a condition of approval of this NDA to retrospectively analyze the safety databases of Study 01 and Study 02 to identify risk factors for increase in creatinine and eGFR associated with bowel preparation for colonoscopy. Because there may be important information that might help identify risk factors in the clinical records of these patients, such as the vital signs during sedation for colonoscopy and the volumes of fluid administered during the procedure, this PMR will state that additional relevant clinical data not captured in the CRF should be sought to include in this retrospective analysis.

Orthostatic Changes

The reviewers examined the orthostatic blood pressure and pulse data from Study 01 and Study 02 for evidence of dehydration. The proportion of patients who had evidence of orthostatic changes on the day of colonoscopy was similar between treatment groups, 20%. The major manifestation was orthostatic change in pulse. Interestingly, approximately 15% of patients had orthostatic changes documented on the 24-48 hour post endoscopy visit and at the

one week post endoscopy visit. I agree with the CDTL that this suggests that dehydration is under recognized at the endoscopy visit or that it is assumed that patients will adequately rehydrate post procedure. The concomitant medication database included some patients who had various volumes of IV fluid recorded as a concomitant medication with their endoscopy sedation medications. Those patients were the minority. It is not clear whether this reflected minimal use of IV fluids during the procedure, or variability among sites in deciding what to record as a concomitant medication (whether to include the IV fluids as a concomitant medication). These observations are of interest in light of the creatinine and eGFR changes discussed above.

ECG Changes

The DB7 reviewer included the following table in his review, summarizing adverse events of cardiac arrhythmia in the clinical trials. There were a number of patients with conduction disorders (AV block and bundle branch block), primarily in the Prepopik arms of the study, and primarily in Study 02. Hypermagnesemia has been reported to cause conduction disturbances. The reviewers examined the laboratory values of these patients and none had hypermagnesemia.

Table 22. Adverse events associated with the SMQ cardiac arrhythmia

	Study-01		Study-02	
	Prepopik (N=305)	HalfLytely (N=298)	Prepopik (N=296)	HalfLytely (N=302)
Adverse Event	n	n	n	n
Atrioventricular block first degree	0	0	3	1
Bundle branch block bilateral	0	0	1	0
Bundle branch block left	1	0	1	0
Bundle branch block right	0	0	2	0
Conduction disorder	0	0	0	1
Electrocardiogram QT prolonged	0	0	1	0
Electrocardiogram change	1	1	0	0
Heart rate irregular	0	0	0	1
Palpitations	0	0	1	0
Syncope	0	0	1	1
Tachycardia	0	0	0	1
Ventricular extrasystoles	1	0	0	1

Ischemic Colitis.

The clinical reviewers evaluated the clinical trial and ex-US postmarketing safety data for evidence of ischemic colitis. OSE was also consulted. The picosulfate component of this product has the same active metabolite of the bisacodyl component of Halflytely. The comparator Halflytely product containing bisacodyl 10 mg was an approved product when these trials were initiated (May 2010). Subsequently, it was removed from the market and replaced by a lower dose bisacodyl (5 mg) product after clinical trials were reviewed that indicated that the lower dose product had similar efficacy. Removal occurred after the July 2010 approval of the Halflytely 5 mg product. The last patient was enrolled in the Prepopik trials in October 2010. At the time of the Halflytley 5 mg bisacodyl product review concerns existed about ischemic colitis associated with the Halflytely with bisacodyl 10 mg product. A

Halflytely product that contained 20 mg bisacodyl had previously been removed from the market for ischemic colitis. Despite its subsequent removal from the market, the Halflytely 10 mg product is an acceptable comparator arm to support this application. The single safety issue allows for a comparison of safety that incorporates an assessment of whether there is evidence of comparability for the safety concern at issue. Evidence to suggest comparability for ischemic colitis would raise safety concerns that would impact the risk/benefit assessment of Prepopik. However, it must be acknowledged that the combined event rate of ischemic colitis for Halflytely bisacodyl 10 mg in the clinical trial that supported its approval and in its postmarketing period was low, and the Prepopik registration trials (Study 01 and Study 02) were not designed as superiority trials to assess this particular safety issue. The trials that were the basis for approving the Halflytely products containing lower doses of bisacodyl (initial 10 mg trial and the subsequent 5 mg trial) were also not designed to demonstrate superiority of the lower dose product on risk of ischemic colitis. Their designs were intended to demonstrate noninferiority in efficacy to the marketed higher dose Halflytely with bisacodyl product associated with ischemic colitis. Reviewers relied upon postmarketing safety data to assess risk of ischemic colitis with each marketed Halflytely product. The low event rate of ischemic colitis with Halflytely with bisacodyl 10 mg would necessitate conduct of a very large clinical trial to establish that Prepopik is superior to the Halflytely (10 mg) product. For this reason, review of the ex-USA postmarketing data for evidence of a higher than background rate of ischemic colitis associated with the magnesium citrate/picosulfate combination product was of particular importance in this NDA.

There were no reports of ischemic colitis in the two randomized, controlled trials submitted in the NDA. Although there were a total of 5 non-serious adverse events of rectal bleeding, intestinal bleeding, and gastrointestinal bleeding reported in subjects treated with Prepopik, the clinical reviewers conducted a detailed review of the clinical presentation and course and found that each case was inconsistent with what is typically seen with IC.

The applicant reported a cumulative world-wide patient exposure for the PREPOPIK formulation from sales through December 31, 2011, of approximately 28,755,398 treatments and the cumulative patient exposure for sodium picosulfate alone over the same time period of approximately 39,518,865 defined daily doses. The original approval outside the US was in 1980, according to the applicant.

The reviewers requested a search of the Ferring Global Safety database for ischemic colitis cases associated with 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 terms included “gastrointestinal hemorrhage” (identified 6 cases) and “ischemic colitis” (identified 16 total post marketing cases, of which 4 were cases identified in the gastrointestinal hemorrhage search). Five of these cases were associated with use in patients with intestinal obstruction, a contraindication to PREPOPIK use, and 1 case was associated with use for an off-label indication, i.e., treatment of severe impaction. Most reports had either limited additional information on the events or the patients had other confounding factors that make attribution of the symptoms solely to the use of the drug difficult.

Based on the usage data of 28 million treatments worldwide, the reviewers concluded that reporting of ischemic colitis (or associated events) is very infrequent and not clearly different than the estimated background rate. A recent OSE evaluation of ischemic colitis associated with the Halflytely with 10 mg bisacodyl product identified a total of 4 cases, including one that occurred in the context of a clinical trial. The search covered the period from May 2009 to December 2011. During the time frame of November 2009 to January 2010 (the lower dose 5 mg product was approved in July 2010) the estimated use, based on number of the Halflytely (10 mg) kits distributed was 368,469. Furthermore, while the active metabolite of sodium picosulfate is identical to that of bisacodyl. it seems inappropriate to entirely extrapolate the safety concerns associated with bisacodyl in combination with PEG to a product that contains a different combination of active ingredients, such as the combination with magnesium citrate in Prepopik.

The reviewers considered it appropriate to include information on ischemic colitis in Warning and Precautions, as it is found in other bowel cleansing product labels. In addition, ischemic colitis will be included in the postmarketing safety information in the product label. I concur with this recommendation and concur with the reviewers' plan to monitor for ischemic colitis in postmarketing spontaneous reporting.

9. Advisory Committee Meeting

There was no Advisory Committee convened to discuss this application because::

A) this drug is not the first in its class

B) the safety profile is similar to that of other drugs approved for this indication C) the clinical study design is similar to previously approved products in the class

D) evaluation of the safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class

E) the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease

F) outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

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

The plan was presented to the Pediatric Review Committee (PeRC) on 5/30/2011. The PeRC and the clinical reviewers agreed with a partial waiver for patients less than 6 months. They did not agree to a waiver for children between 6 months and 2 years. Nulytely is a bowel cleansing product that has pediatric labeling down to 6 months of age. A decision was made to defer the conduct of pediatric studies in children 6 months of age and older.

Subsequent to the PeRC meeting the reviewers questioned the adequacy of the information to support dose selection for children. The product has pediatric labeling (including dose) in the UK (Picolax; 1985) and Canada (Pico-Salax; 2004). Although the product is used with these dose instructions outside the US, the reviewers found that the doses were based on clinical experience in centers that had used the product to treat children. The Clinical reviewer noted that Turner and colleagues[4] found the Canadian labeled pediatric dosing to be safe and effective in a randomized trial that enrolled 89 pediatric patients ages 4 – 18 years and compared Pico-Salax to PEG-ELS. Based on this, the CDTL and the PMHS staff suggested that it would be worthwhile to explore more than just the dose currently used outside the U.S. in the pediatric trials. The reviewers also noted that a recently approved pediatric plan of a bowel cleansing product included both dose exploration and an active comparator design. The reviewers recommended that the pediatric plan for Prepopik should incorporate a Nulytely control arm, to enhance interpretation of the safety findings in the studies. The reviewers discussed the fact that selection of additional doses to explore in each age group may be challenging, balancing the potential safety issues (for higher doses) and efficacy issues (lower doses could be a concern if they resulted in unacceptable bowel cleansing); however, the protocols could be designed with careful monitoring by a DSMB with early stopping rules to address these issues. The Division can involve Pediatric Ethics staff in future protocol review.

During the course of this discussion, pediatric gastroenterology reviewers challenged the selection of 6 months as the lower age for study. They stated clear liquids are often utilized for this age group, and that patients as young as 1 year who require a colon cleansing procedure that involves a cathartic are often managed in an inpatient setting. A literature review was conducted to support this position. Additionally, the clinical trial evidence to support Nulytely dosing in young children was examined, and the reviewers noted its pediatric dosing was based on literature reports. The PMHS reviewers concurred with the pediatric gastroenterology reviewers from the division that a Nulytely comparator arm should not be required. I concur with this recommendation and that studies should be waived under the age of 1 year.

Although the CDTL noted that at the time of his review the nonclinical team was considering whether additional juvenile toxicity (animal) studies are needed. The nonclinical team concluded that additional juvenile animal studies are NOT needed.

The reviewers returned to PeRC on July 11, 2012, to present the new proposed pediatric plan. The PeRC concurred with the plan to waive pediatric study requirements for birth to 12 months and to defer submission of pediatric studies for children over the age of 12 months.

The following pediatric studies will be required under PREA:

1902-1. Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 9 years to 16 years). This study will include PK assessments.

[4] 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.

a. Final Protocol Submission: February 2013
b. Study Completion: February 2016
c. Final Report Submission: August 2016

1902-2. Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 2 years to <9 years). This study will include PK assessments.

a. Final Protocol Submission: February 2016
b. Study Completion: February 2019
c. Final Report Submission: August 2019

1902-3. PREA Study 3: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 12 months to <2 years). This study will include PK assessments.

a. Final Protocol Submission: February 2018
b. Study Completion: August 2019
c. Final Report Submission: February 2020

11. Other Relevant Regulatory Issues

Three clinical sites were inspected by DSI. The DSI review concluded that the data from all 3 sites appeared reliable and could be used in support of the NDA.

The Applicant provided a signed 3454 form for Certification of Financial Interests and Arrangements of Clinical Investigators denying any financial arrangements with the clinical investigators from the sites that performed the clinical trials Study 01 and Study 02, as defined in 21 CFR 54.2(a).

The Combination Policy has been adequately addressed in this NDA. It was determined that a full factorial study would not be required to address the combination rule. Both components to this combination product are cathartics with different mechanisms of action that each have colon cleansing effects. After examining the literature for evidence of the effectiveness of each component for colon cleansing, the reviewers concluded that a full factorial study could not be conducted due to serious ethical concerns because the literature review indicated that each component as a stand alone would result in inadequate colon cleansing for colonoscopy. The basis for this decision is described below:

Adequate visualization of the colonic mucosa is key to identification and removal of malignant lesions and adenomatous polyps. Missed lesions can result in diagnosis of interval

colon cancers, between screening endoscopies. These malignant tumors arise from lesions that were likely missed in the prior screening examination.[5,6] In addition, a subtype of polyps, sessile serrated polyps, are flat, which makes them particularly challenging to visualize.[7] Without an adequate bowel preparation there is a higher likelihood that such lesions could be missed. Therefore, a patient subjected to a bowel preparation expected to be inadequate at study initiation places that patient at increased risk of undergoing a procedure in which a polyp or malignancy is missed. Additionally, the procedure itself involves serious risks related to sedation and the procedure itself. Exposure of a patient to such risk, while knowing that the patient has undergone an inadequate bowel preparation and will require the procedure to be repeated, raises ethical concerns.

In order to determine whether there is evidence that each component of Prepopik could be expected to provide inadequate colon cleansing as a stand alone product, the Division conducted a literature review. The reviewers also examined the lower bounds of the confidence intervals for the proportion of successful preps (excellent + good) for various recently approved bowel preparations in order to set what could be considered reasonable evidence of an adequate bowel preparation to allow study in a clinical trial. They selected 70% as the lower bound that must be exceeded for a same day prep administration schedule, and 80% as the lower bound that must be exceed for the split dose administration schedule.

The publications in the table below were identified 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, the reviewers relied upon available literature on bisacodyl's use in bowel preparation for colonoscopy. Relative exposures to sodium picosulfate, based on the active metabolite of both products, are included in the table.

Confidence intervals were calculated based on the proportion of patients who were identified as having a good or excellent prep in 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 for if the same response rate had been observed in a larger sample size. This exploration was pursued in light of the very small sample size in some of these studies.

[5] Leung et al, Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointestinal Endoscopy, Vol.71,No1:2010, 111-117.
[6] 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.
[7] Rex DK, Ahnen DJ, et al. Serrated Lesions of the Colorectum: Review and Recommendations From an Expert Panel. Am J Gastroenterology. June 19, 2012.

Table 23: Summary of Literature

Bisacodyl	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) Adjusted to 107/200 (46,61) Adjusted to 161/300 (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) 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 (paper says 3 pills taken twice) the day prior to colonoscopy + 3000 cc water	38.8% = 19/49 CI(25,54) 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) 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 3 days prior]	34 /136 = 25% CI (17,33) adjusted to 50/200 CI(19,31) adjusted to 75/300 CI (20,30)	
Magnesium citrate	**Picolax contains** (b) (4)		
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) 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) 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 (<u>TOTAL of **51g**</u>) on the day prior to colonoscopy [PLUS clear liquid diet the day prior]	94%* = 131/140 CI(88,97) 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) Adjusted to 135/200 CI(61,74) Adjusted to 203/300 CI(62,73)	**NONRANDOMIZED AUDIT** <u>Good + Satisfactory</u> Satisfactory = small amounts of feces or fluid not interfering with the exam.
Arm 2 of Vradelis	Magnesium citrate 35g split dose + <u>**SENNA**</u> (the day prior). [PLUS low residue diet followed by a clear liquid diet]	148/182 = 81% CI(75,87) Adjusted to 163/200 CI(75,87) Adjusted to 244/300 CI(77,86)	**NONRANDOMIZED AUDIT** **Arm 2**

All four bisacodyl publications studied bisacodyl doses higher than the 14 mg dose predicted to produce the same amount of active metabolite as sodium picosulfate. In addition, these studies utilized other means of colon cleansing and all utilized dietary changes of variable durations. Enemas were utilized in two (Rasmussen et al. and DiPalma); however, it is generally accepted that enemas would not be expected to adequately cleanse the right colon. In DiPalma, the bisacodyl was combined with a magnesium citrate dose that is lower than in Prepopik. The Wang, et al, publication from a Chinese Veterans hospital did not report "good + excellent"; instead, proportions of "very good + good" were reported. The authors also included a category of "average". Inclusion of this category was also explored but it is unclear what this category was, Because it may be comparable to the more commonly utilized label in the publications, "fair", the Division did not rely on the analysis incorporating "average" for a decision regarding evidence of efficacy.

The lower bound of the confidence intervals around the point estimate for proportion of responders (defined as good + excellent preps) treated with bisacodyl fell below 70%, even in the exploratory analyses utilizing predicted confidence intervals based on higher sample sizes. There was one exception, but only in the exploratory analyses. In the DiPalma publication, the lower bound of the confidence intervals in the exploratory analyses reached 73 and 74; however, these were exploratory analyses and this study arm also incorporated magnesium citrate and an enema the morning of the colonoscopy. The trial was included in this analyses because the magnesium citrate dose was lower than that in the combination product of interest; however, this factor and the exploratory nature of the confidence intervals in question makes this observation unreliable. The Wang, et al publication had an a lower bound of the confidence interval that reached 70 in one of the exploratory analyses; however, this occurred only in one of the analyses that included the "average" rating in the responder definition. The concern about including this category was discussed above.

None of the 3 magnesium publications utilized the magnesium citrate dose of Prepopik. In two, the dose was exceeded, and in one (DiPalma, et al) it fell below. In addition, other means of cleansing the colon were utilized to clear in the colon, including dietary changes of variable durations and enemas. 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 confidence intervals around the point estimate for proportion of responders (defined as good + excellent preps) treated with magnesium citrate fell below 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 studies utilized magnesium citrate doses that exceeded Prepopik, and the Vradelis arm also exposed patients to the stimulant laxative senna. The latter study was not a randomized trial, and the bowel cleansing score designation differs from the other publications. For these reasons the apparent "favorable" outcomes observed in these studies do not support the ethical conduct of a full factorial study.

Excluding the Berkelhamer 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 that exceeded 70%. This arm also contained an enema plus low residue diet X 3 days. This exploratory finding 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. This magnesium citrate/senna arm would be expected to have a higher treatment effect; however, the lower bound did not exceed 70%. This raises concerns regarding the magnitude of the treatment effect of magnesium citrate in this exploratory analysis. Based on this review, the reviewers determined that available data do not support that each component of Prepopik could be expected to provide adequate bowel cleansing as a stand alone product.

12. Labeling

DMEPA conducted name reviews and determined that the applicant's original proposed name, Picoprep, was unacceptable. The applicant submitted a request for review of an alternative proposed name, Prepopik, which DMEPA concluded was acceptable.

See other sections of this review and the CDTL review for additional labeling review issues and recommendations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval
- Risk Benefit Assessment – All review disciplines have recommended approval. I agree with the reviewers' recommendation that the product labeling should clearly state that the split dose regimen is the preferred regimen. The safety review did not identify new safety issues associated with this new colon cleansing product. The serum chemistry changes appeared comparable to what has been observed with other marketed bowel cleansing products and the labeling for Prepopik will carry those same warnings. There will be an additional contraindication in Prepopik's labeling for patients with severe renal insufficiency due to the potential for accumulation of magnesium because it contains substantially more magnesium than other bowel cleansing products. The evidence of changes in creatinine and eGFR observed in the two clinical trials submitted in this application (in both treatment arms) have also been observed in other studies of bowel cleansing products. The applicant has committed to conducting a PMR study under FDAAA to further evaluate the data from these trials and to seek additional clinical data from the patients in the trial in an effort to better define risk factors for developing these changes in renal function.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The reviewers have not recommended a REMS and I concur that there is no reason to require a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

To assess a signal of a serious risk of renal insufficiency, as a condition of approval the Applicant will be required under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to conduct the following:

1902-4 Conduct a retrospective study to identify the risk factors associated with development of persistent deterioration of renal function in patients undergoing colon cleansing with Prepopik in preparation for colonoscopy.

This study should evaluate all available data for all patients at any point during studies FE2009-01 and FE2009-02, including relevant clinical data not recorded in the CRF such as volume of fluid administered during the colonoscopy and vital signs recorded during the colonoscopy. Identify those patients with a decrease in renal function and compare any difference in risk factors or clinical status with those patients who did not have renal dysfunction.

Evaluate any patient who had a decline in renal function as measured by a decline in eGFR at the Day 30 assessment by collecting additional information with regard to renal function beyond the Day 30 assessment including concomitant medication use, additional procedures, and inter-current illness.

In addition, the applicant will be required to conduct the pediatric studies under PREA described in Section 10 Pediatrics of this review.

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

/s/

DONNA J GRIEBEL
07/16/2012