CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202535Orig1s000

OFFICE DIRECTOR MEMO

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 16, 2012

TO: NDA 202535
PrepoPik (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution
Ferring Pharmaceuticals, Inc.

FROM: Victoria Kusiak, M.D.
Deputy Director, Office of Drug Evaluation III

SUBJECT: Approval Action

PrepoPik (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution is a stimulant and osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. While sodium picosulfate is itself pharmacologically inactive and undergoes very slow absorption, it is converted to the pharmacologically active metabolite, bis (*p*-hydroxyphenyl)-2-pyridylmethane (BHPM) by gut microbes through bacterial hydrolase. Sodium picosulfate is the primary active component of PrepoPik and constitutes 0.06% of the 16.1 g PrepoPik drug product. The product also contains magnesium oxide (22%) and citric acid (74%) which form magnesium citrate in water solution. The laxative effect of sodium picosulfate is attributable to an inhibition of water absorption in the colon, caused by the BHPM metabolite. When the product is dissolved in water, the magnesium oxide and the citric acid combine to form magnesium citrate, which is an osmotic laxative.

Citric acid and magnesium oxide are extensively used in food products and in over the counter (OTC) pharmaceutical products in the US. Sodium picosulfate is marketed in several countries outside of the US as a stimulant laxative. This product has been approved and is marketed in 38 countries including the United Kingdom, Ireland and Canada.

One dose of PrepoPik consists of 2 pouches of powder for oral solution, each dissolved in 5 ounces of cold water and administered at separate times. Additional fluids must also be consumed before, during and after consumption of PrepoPik.

This memorandum documents my concurrence with the Division of Gastroenterology and Inborn Error Products (DGIEP) to approve PrepoPik (2 pouches, each of which contains 10 mg sodium picosulfate, 3.5 mg magnesium oxide and 12 grams anhydrous citric acid;

to be taken on separate occasions) for the cleansing of the colon as a preparation for colonoscopy in adults. PrepoPik should be taken as a split dose regimen in which the first pouch is taken the night before colonoscopy and the second is taken the next day, in the morning, prior to colonoscopy; alternatively, if necessary PrepoPik can be taken as a day before regimen in which the first pouch is taken in the afternoon or early evening and the second is taken approximately 6 hours later, the night before colonoscopy. Additional fluid is also required to be taken.

REGULATORY HISTORY

A Pre-IND meeting between Ferring Pharmaceuticals, Inc. and DGIEP was held on April 16, 2009 during which the following was noted:

- The applicant would be required to conduct the complete battery of reproductive toxicity studies
- A 9% non-inferiority margin should be used in clinical trials as opposed to a 15% non-inferiority margin
- As the product contains two or more drugs, evidence will be required to show that each component makes a contribution to the claimed effects (cf.21 CFR 300.50). The applicant stated that the usual evidence provided by factorial designed clinical trials would not be appropriate in this case because it is known that use of only one of the components for bowel preparation does not work. As the patients involved in trials would be using the study drugs as a bowel cleanse in preparation for colonoscopy, it would be unethical to have the patients in the trial receive an agent known to be ineffective. FDA stated that a factorial designed clinical development was not required, but that evidence must be provided to support the need for the combination. If the applicant claims that neither component would work alone, convincing evidence supporting that assertion would need to be provided.
- If there is substantial systemic exposure of sodium picosulfate, *in vitro* studies including studies of transporters and CYP 450 enzymes will be required in order to determine the need for *in vivo* drug-drug interaction studies. If sodium picosulfate is determined to be bioavailable, a thorough QT study would be recommended.

The IND for PrepoPik was filed by Ferring Pharmaceuticals, Inc. on February 22, 2010. Two phase 3 protocols were filed along with the IND. Numerous Advice Memorandums concerning the phase 3 protocol designs were provided by DGIEP between March 25, 2010 and October 25, 2010, after which the Phase 3 protocols were agreed upon.

On January 5, 2011, an Advice Letter was provided to the applicant addressing a protocol amendment and a statistical analysis plan sent for review in April/May of 2010. At this time a 4% non-inferiority margin was suggested since a 9% margin might result in a 10.6% relative decrease in the assumed event rate of 85% for the test drug as compared

to the control, while a 4% margin would result in a 5% decrease in the event rate for the test drug.

A Pre-NDA meeting was held on March 21, 2011 during which the format of the NDA was agreed upon. Additionally, the applicant was informed that while the phase 3 studies did not appear to show evidence of cardiac arrhythmias associated with the use of PrepoPik, the studies were not powered or designed to rule out a specific cardiac safety signal and as such, in the absence of an adequately designed clinical program to evaluate this issue, the product label would be subject to class labeling with regard to cardiac risk secondary to electrolyte imbalance.

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

The NDA for sodium picosulfate was submitted on September 16, 2011.

CHEMISTRY MANUFACTURING and CONTROLS

There are no outstanding CMC issues. The proposed testing and acceptance criteria for both the drug substance and the drug product are considered adequate to assure identity, strength, purity, and quality for PrepoPik.

CLINICAL MICROBIOLOGY

There are no clinical microbiology issues for this application.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Overall, nonclinical safety studies conducted with PrepoPik provide adequate assurance of its safety and support its proposed use at the intended therapeutic dose and in accordance with the proposed product labeling.

The applicant has conducted 14-day oral toxicology studies in rats and dogs with sodium picosulfate as well as 28-day oral toxicology studies in rats and dogs with PrepoPik. Additionally, genotoxicity studies (Ames test, mouse lymphoma assay and *in vivo* mouse micronucleous test) were conducted with sodium picosulfate and reproductive toxicology studies (assessing fertility and early embryonic development to implantation [Segment I] in rats, embryofetal development [Segment II] in rats and rabbits, and pre- and postnatal development [Segment III] in rats) were conducted with PrepoPik.

When sodium picosulfate (the principle ingredient in PrepoPik) was administered orally for up to 14 days at doses 6000 times the maximum recommended Human Dose (MRHD) in rats and up to 3600 times the MRHD in dogs, treatment related clinical signs included soft stools, diarrhea, and fecal staining, as anticipated. Treatment related clinical chemistry findings included decrease in electrolytes (sodium, potassium and chloride). In rats, sodium picosulfate causes increase in thickness of the intestine at all doses with minimal to mild mucosal hyperplasia of the small and large intestine. Mucosal

hyperplasia associated with lymphocytic infiltration was seen in the small intestine at 1800 times the MRHD.

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

Literature references for sodium picosulfate showed no treatment related adverse effects on mating and fertility performance of rats at up to 100 mg/kg/day (approximately 300 times the MRHD). In rats, sodium picosulfate was not teratogenic at doses up to 10,000 mg/kg/day (approximately 3000 times the MRHD). In rats at 100 mg/kg/day, there were an increased number of dead pups at birth.

In the 28-day oral toxicity studies the no observed adverse effect levels (NOAELs) for PrepoPik were 8 times the MRHD in rats and 4 times the MRHD in dogs. No effect was seen on male or female fertility in rats at doses up to 1.2 times the MRHD. At doses 1.1 times the MRHD there was no evidence of harm to the fetus. No adverse effect was seen on pre- and postnatal development at doses 1.2 times the MRHD.

The labeling for PrepoPik will contain the statements that while animal studies have been conducted in rats and rabbits at doses up to 8 and 4 times the human dose respectively, and revealed no evidence of impaired fertility or harm to the fetus due to PrepoPik, there are no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response, PrepoPik should be used in pregnancy only if clearly needed.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Sodium picosulfate, the principle ingredient in PrepoPik, is a pro-drug which is converted to its active metabolite BHPM, by colonic bacteria. After administration of 2 pouches of PrepoPik separated by 6 hours, picosulfate reaches a mean Cmax of 3.2ng/ml at approximately 7 hours (Tmax). After the first pouch, the corresponding values are 2.3 ng/ml at 2 hours. The terminal half-life is 7.1 hours. The fraction of the absorbed sodium picosulfate dose excreted unchanged in the urine is 0.19%. Plasma levels of the free BHPM are consistently low with 13 out of 16 subjects studied having plasma BHPM concentrations below the lower limit of quantification (0.1 ng/ml).The majority of the excreted BHPM is in the glucuronide-conjugated form. Magnesium oxide and citric acid react with water to form magnesium citrate, which is only minimally absorbed from the gastrointestinal tract. Peak magnesium concentration (Cmax) was 1.9 mEq/L and occurred 10 hours after initial pouch administration.

The exposure of the active metabolite (BHPM) in plasma was lower compared to the parent compound, picosulfate. As only 3 of 16 subjects had quantifiable levels (assay lower limit of quantification 0.1 mg/ml) of BHPM in plasma, a through PK analysis was not possible.

Pharmacodynamics: Sodium picosulfate has a stimulant laxative activity, which, when combined with the osmotic laxative activity of magnesium citrate, produces a duel action purgative effect, which in the presence of additional ingested fluids, produces a watery diarrhea.

Drug Interactions: The applicant evaluated the potential drug interactions with sodium picosulfate by assessing its potential to act as an inhibitor or inducer of the major drug-metabolizing cytochrome P450 enzymes in *in vitro* studies. Sodium picosulfate does not appear to be a direct, time dependant or metabolism dependant inhibitor of any of the CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) evaluated. Studies in cultured human hepatocytes showed that sodium picosulfate is not an inducer of CYP1A2, CYP2B or CYPA4/5 at concentrations up to 1.8 μM. Based upon these results, it was determined that no *in vivo* drug-drug interaction studies were necessary.

It was noted that sodium picosulfate may reduce the absorption of co-administered drugs by decreasing gastrointestinal transit time secondary to its laxative effect. Therefore, oral medication should not be given within 1 hour of the administration of sodium picosulfate.

Thorough QT study: The applicant requested a waiver of a thorough QT study. The QT/IRT team, concluded that as sodium picosulfate has some bioavailability, a thorough QT assessment should be conducted to determine what effects sodium picosulfate may have on the QT interval. However, the systemic exposure at the therapeutic dose is so low that markedly supratherapeutic doses would be required in order to achieve levels commensurate with the potential to cause a shift. These doses could be expected to cause major fluid and electrolyte shifts which in and of themselves might be expected to impact the QT interval without regard to the effect of PrepoPik. Additionally the patients' physiological response to supratherapeutic doses would be such as to render such a study unethical. Therefore the thorough QT study is waived.

Special Populations: Geriatric use: In controlled clinical trials of PrepoPik, 18% (215/1201) of patients were 65 years of age or older. The overall incidence of treatment emergent adverse reactions was similar among patients ≥65 years of age (73.2%) and patients, < 65 years of age (71%). The incidence of nausea and headache tended to be lower in the ≥65years of age group (1.8% each) as compared to the younger patients (4.9% and 4.3%, respectively). No overall difference in effectiveness was noted, with 81.1% of patients ≥65 years of age having successful bowel cleansing as compared to 70.9% in the younger group.

Renal and Hepatically Impaired: Sodium picosulfate was not evaluated in patients with moderately severe or severe renal failure or in hepatically impaired patients, as the agent is intended for single dose administration. While phase 3 clinical trials included 379 patients with mild to moderate renal impairment (creatinine clearance < 90 mL/min), pharmacokinetic parameters were not measured in these patients, so no comparison to patients with normal renal function can be made. Labeling will include warnings for use in these populations consistent with those of other colon cleansing agents. Use of PrepoPik will be contraindicated in patients with severe renal failure because of the possibility of the development of hypermagnesemia in this population secondary to the increased magnesium load imposed by the magnesium oxide component of the product.

EFFICACY

The colon cleansing efficacy of PrepoPik was evaluated for non-inferiority against a comparator (Halflytely)[1] in two randomized, investigator blinded, active controlled multicenter US trials in patients scheduled to have an elective colonoscopy. In all, 1195 adult patients were evaluated: 601 from Study 1 and 594 from Study 2. The mean patient age was 55.9 (range 18-80) with 61% female and 39% male and 89.5% White, 9.8% Black, and 0.7% other. Of these, 2.8% self identified as Hispanic.

Patients in the two trials were randomized to one of two different dosing regimens:

- Study 1 (Split Dose): The first pouch of PrepoPik was taken the evening before colonoscopy followed by 5 glasses (8oz each) of clear liquid; the second pouch was taken the morning of the colonoscopy (5-9 hours prior to colonoscopy) followed by 3 glasses (8 oz each) of clear liquid.
- Study 2 (Day Before): Both pouches were taken separately on the day before colonoscopy, with the first pouch taken in the afternoon between 4 and 6 PM followed by 5 glasses (8 oz each) of clear liquid, and the second pouch taken in the late evening (approximately 6 hours after the first pouch) followed by 3 glasses (8oz each) of clear liquid.

The comparator in both trials was a preparation containing 2 liters of polyethylene glycol plus electrolytes solution (PEG+E) and 2 bisacodyl 5 mg tablets administered the day before the procedure. All patients were limited to clear liquids the day before the procedure (24 hours before).

The primary efficacy endpoint was the proportion of patients with successful colon cleansing as assessed by blinded colonoscopists using the Aronchick Scale. Successful colon cleansing was defined as bowel preparations with > 90% of the mucosa seen and mostly liquid stool that were graded excellent (minimal suctioning needed) or good (significant suctioning needed) by the colonoscopist.

PrepoPik was non-inferior to the comparator in both trials (9% non-inferiority margin). In addition, the PrepoPik split dose regimen was found superior to the comparator by the pre-specified criteria for superiority. The proportion of patients with successful colon cleansing in Study 1 (Split Dose) was: PrepoPik Split Dose, 84.2% (256/304); Comparator 74.4% (221/297) with 9.8% difference and a one sided 97% confidence interval of 3.4% (i.e., non-inferior and superior). The proportion of patients in Study 2 (Day Before Dosing) with successful colon cleansing was: PrepoPik 83.0% (244/294), Comparator 79.9 % (239/300) with a 3.3% difference and a one sided confidence interval of -2.9% (non-inferior).

All but 4 patients completed the PrepoPik dosing regimens (N=596) as opposed to 53 that did not complete dosing in the comparator group.

[1] Halflytely (polyethylene glycol [PEG] 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 mg [10 mg bisacodyl] was considered an appropriate comparator for the purpose of demonstrating efficacy at the time the clinical trials for PrepoPik were designed. Subsequent to the initiation of clinical trials with PrepoPik, on July 16, 2010, Halflytely was withdrawn from the market and placed on the Discontinued Drug Product List of the Orange Book. On June 22, 2011, DGIEP determined that Halflytely was withdrawn for reasons of safety. (Federal Register/Vol.76, No. 159/ Wednesday, August 17, 2011/ Notices Pg 51037-51038.). Halflytely remains a valid comparator for demonstration of the efficacy of PrepoPik.

SAFETY

Clinical Trials Experience:

In randomized, multicenter, controlled trials, nausea, headache and vomiting were the most common treatment emergent adverse reactions (>1%) following PrepoPik administration. Because abdominal bloating, distension, pain/cramping, and watery diarrhea are expected to occur with colon cleansing, these effects were documented as adverse reactions in the clinical trials only if they required medical intervention. The mean age of patients evaluated was 56 years (range 18-80 years) with 61% females, 39% males, 89.5% White, 9.8% Black and <1% other.

In Study 1 (Split Dose), nausea occurred in 2.6% of the PrepoPik treated subjects as compared to 3.7% in the control group. Likewise for headache, the incidence was 1.6% in the PrepoPik group as compared to 1.7% in the control group. The incidence for vomiting was 1.0% and 3.4% respectively for the PrepoPik group versus the comparator. For Study 2 (Day Before Dosing) the incidence was: nausea 3.0% with PrepoPik compared to 4.3% with comparator; headache 2.7% with PrepoPik compared to 1.7% with comparator, and vomiting 1.4% with PrepoPik compared to 2.0% with comparator.

In Study 1 (Split Dose), 1/211 (0.3 %) of subjects experienced a serious adverse event with PrepoPik as opposed to 2/217 (0.7%) in the comparator group. The single subject in the PrepoPik group who had a serious adverse reaction developed pancreatitis which was assessed by the investigator as being unrelated to study drug. Likewise in Study 2 (Day Before Dosing), 2/305 (0.7%) of subjects in the PrepoPik group as opposed to 1/298 (0.3%) in the comparator group experienced a serious adverse event. Of the two PrepoPik subjects who experienced serious adverse events, one subject had colon cancer and dehydration and the second had acute coronary syndrome with stent placement. Neither event was considered by the investigator to be related to study drug. There were no deaths in the trials.

Electrolyte Abnormalities:

In general, the PrepoPik Split Dose regimen was associated with numerically higher rates of abnormal electrolyte shifts on the day of colonoscopy compared to the preparation containing 2 Liters of PEG+E plus two 5 mg bisacodyl tablets. These shifts were transient in nature and numerically similar between treatment arms at the day 30 study visit. PrepoPik is associated with an increase in serum magnesium (due to its magnesium oxide component); however, the small mean changes from baseline are clinically insignificant.

In individual patients taking PrepoPik there is a risk of significant fluid and electrolyte abnormalities, arrhythmias, seizures and renal impairment possibly due to the combination of electrolyte shifts and dehydration. These risks are common to all bowel cleansing products and will be noted in labeling.

Renal Function Analysis:

An analysis of renal function based upon creatinine and eGFR (estimated glomerular filtration rate) was performed for patients in both trials (combined data) across study visits. The purpose of this analysis was to investigate further the observation that some patients had abnormally high serum creatinine at Day 30 post exposure to PrepoPik, but normal creatinine values on previous visits and at baseline.

The following table presents the increase in mean creatinine on the day of colonoscopy (visit 3) for those patients with normal creatinine at baseline and abnormal creatinine on the day of colonoscopy. The mean creatinine values for those with normal creatinine at baseline and on the day of colonoscopy are presented for comparison.

Mean Increase in Creatinine (mg/dl) for Patients with Normal Baseline Creatinine and Abnormal Visit 3 Creatinine

Treatment	Category	n	Mean Increase in Creatinine from baseline
Comparator	Normal at baseline to High at Colonoscopy	29	0.13
PrepoPik		**17**	**0.19**
Comparator	Normal at baseline to Normal at Colonoscopy	505	0.02
PrepoPik		**505**	**0.02**

These data suggest that a small subgroup of patients had relatively small increases in serum creatinine on the day of colonoscopy, possibly due to dehydration.

The following table presents the mean increase in creatinine at Day 30 for patients who had normal creatinine values at baseline and on the day of colonoscopy, but abnormal values on Day 30. The number of patients is small.

Mean Creatinine Increases (mg/dl) in Patients with Normal Creatinine on Day of Colonoscopy and Abnormal Creatinine at Day 30

	n	Mean Increase in Creatinine from Baseline
Comparator	14	0.15
PrepoPik	**22**	**0.24**

The following table presents the serum creatinine changes across study visits for those patients identified in the table above. These patients had a normal creatinine on the day of colonoscopy, but abnormal values at day 30. The mean increase in creatinine appears to "spike" only at the Day 30 visit.

Mean Creatinine Increases (mg/dl) in Patients with Normal Creatinine at Day of Colonoscopy and Abnormal Creatinine at Day 30

	n	Day of Colonoscopy	24-48 hours	Day 7	Day 30
Comparator	14	0.004	0.02	0.05	0.15
PrepoPik	**22**	**0.02**	**0.05**	**0.06**	**0.24**

The mean change in eGFRs in the same patients shows a decrease over time that is more apparent in the PrepoPik arm. (See table below).

eGFR (mml/L) Across Study Days for Patients with Normal Creatinine at Day of

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

Colonoscopy and Abnormal Creatinine at Day 30

A review of the individual data for these patients did not reveal a clear trend in individual subjects' eGFR. The trend appears most evident in the mean values for this subgroup. A review of the adverse reaction listings in these subjects did not identify a consistent trend in adverse events associated with changes in creatinine.

Because the clinical significance of these small decreases in renal function seen in a small number of patients 30 days after taking PrepoPik is unknown, a retrospective clinical study to evaluate the effects of PrepoPik on renal function will be required post-marketing.

Post-marketing Experience:

In post marking experience during foreign post-approval use of fomulations similar to PrepoPik in 38 countries involving approximately 28.8 million subjects, the following additional adverse events have been reported: hypersensitivity reactions including rash, urticaria and purpura, hypokalemia, hyponatremia, abdominal pain, diarrhea, fecal incontinence and proctalgia.

There have been isolated reports of mild, reversible aphthoid ileal ulcer and generalized tonic-clonic seizures sometimes associated with hyponatremia in epileptic patients.

These reactions are reported voluntarily from a population of uncertain size. Therefore no reliable estimate of frequency of events or causal relationship to drug exposure can be made.

ADVISORY COMMITTEE

This application was not referred to an Advisory Committee because the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of disease, and outside expertise was not necessary.

REGULATORY ISSUES

During a Type B pre-IND meeting held on April 16, 2009 between FDA and the applicant, the applicant was informed that since the product under development contains two or more components, evidence would be required to demonstrate that each component makes a contribution to the claimed effects of the product (21 CFR 300.50). FDA stated that the applicant's development program would need to give consideration to how it will generate such evidence. FDA noted that such evidence is typically provided by the results of a factorial analysis of the proposed combination ingredients that demonstrates that the combination product is more effective than each component of the combination alone; however, applicants may meet the requirements of 21 CFR 300.50 in other ways. The applicant stated that a factorial study would not be ethical because using one component as monotherapy would not provide sufficient colon cleansing to allow for an adequate colonoscopic evaluation in patients undergoing cancer screening. The applicant was advised to provide evidence in support of the fact that each component would be ineffective on its own and that a combination of ingredients was therefore required.

The applicant supplied published literature evidence of the inadequacy of each component alone as a colon cleansing agent for preparation for colonoscopy and asserted that if adequate colon cleansing cannot be reasonably expected from a single component, then a study evaluating that component as a single agent in a population of subjects undergoing colonoscopy, many of them for cancer screening, would not be ethical.

Colon cancer screening with colonoscopy is performed to detect not only cancer, but pre-malignant lesions (i.e., adenomatous polyps). Detection and removal of these lesions has been shown to prevent future development of colon cancer.[2] Adequate visualization of the colonic mucosa is essential for both the identification and removal of these lesions. Lesions missed during colonoscopy can result in the development of interval colon cancers between screening endoscopies.[3,4] A patient subjected to a bowel preparation

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

[3] Leung et al, Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointestinal Endoscopy, Vol. 71, No 1:2010, 111-117.

known to be inadequate in order to conduct a factorial study would be at increased risk of undergoing a procedure in which a polyp or malignancy is missed. Additionally, a colonoscopy procedure is usually performed under sedation; both the procedure and sedation are associated with risks of serious adverse events. Exposing a patient to such risk while knowing that that patient likely will have undergone an inadequate bowel preparation and therefore potentially an inadequate evaluation, raises serious ethical concerns.

In order to determine whether a full factorial study would be ethical in light of the concerns raised above, DGIEP examined the literature for evidence regarding the adequacy of each component of PrepoPik when used as a single agent. The lower bounds of the 95% confidence intervals for the proportion of responders (defined as patients with successful preps rated good or better) for various recently approved bowel preparations were reviewed. Based upon DGIEP's review, it appeared that in order to conclude that a bowel preparation agent was not potentially inferior to approved products, the lower bound of the 95% CI for the treatment effect should be no less than 70% for regimens administered on a same day schedule, and no less than 80% for regimens administered on a split dose schedule.

The publications in the table below were identified by DGIEP as providing evidence for the efficacy of the individual components, sodium picosulfate and magnesium citrate, in the setting of colonoscopy. Because single agent sodium picosulfate colonoscopy studies were not identified, and because bisacodyl and sodium picosulfate share the same active metabolite, DGIEP relied upon available literature on the use of bisacodyl for bowel preparation for colonoscopy to assess the efficacy of sodium picosulfate.

Bisacodyl (14 mg = 20 mg picosulfate)	**REGIMENS**	**PROPORTION OF RESPONDERS & CONFIDENCE INTERVALS**
Rasmussen, et. al. [Scand J Gastroenterol 2003 (10):1090]	40 mg bisacodyl total dose 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)
Dipalma et al [Gastroenterology 1984;86:856-60]	40 mg bisacodyl total dose 20 mg the day prior to colonoscopy+ 20 mg the night prior to colonoscopy [Plus minimum residue diet x 1 day; 240 cc	80% (35/44) CI (65, 90)

[4] 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.

	(17g) Magnesium citrate the day prior + enema the AM of colonoscopy]	
Wang, et al [J Chin Med Assoc, 2003; 66:364-365]	30 mg bisacodyl(3 pills taken twice) the day prior to colonosocopy + 3000 cc water	38.8% (19/49) CI (25, 54)
Chen, et al [J Chin Med Assoc, 2009; 72 (8):402	Biscodyl 30 mg (6 pills) the night prior to procedure + 2000cc water [Plus low fiber 3 days prior]	25% (34/136) CI (17, 33)

Magnesium citrate	**REGIMENS**	**PROPORTION OF RESPONDERS & CONFIDENCE INTERVALS**
Dipalma et al [Gastroenterology 1984;86:856-60]	Magnesium citrate 240cc (17g) the day prior to colonoscopy [Plus low residue diet x 3 days, enema the night before colonoscopy and the morning of colonoscopy]	80% (32/40) CI (64,91)
Dipalma et al [Gastroenterology 1984;86:856-60]	Magnesium citrate 240cc (17g) the day prior to colonoscopy [Plus clear liquid diet x 3 days, enema the night before colonoscopy and the morning of colonoscopy + 240cc senna]	69% (44/64) CI (56,80)
Berkelhammer et al [Gastrointestinal Endoscospy, 2002, 56:89-94]	Magnesium citrate 300cc (17g) x 3 (Total 51g) the day prior to colonoscopy [Plus clear liquid diet the day prior]	94% (131/140) CI (88,97)
Vradelis, et al. [2009, 15 (14):1759-63):	Magnesium citrate 35g split dose. [Plus senna, low residue diet followed by a clear liquid diet]	68% (108/160) CI (60,75)
Arm 2 of Vradelis	Magnesium citrate 35g split dose + SENNA (the day prior). [Plus low residue diet followed by a clear liquid diet]	81% 148/182 = CI (75,87)

The lower bound of the 2-sided 95% confidence intervals (binomial) around the point estimate for the proportion of responders treated with bisacodyl was less than 70% in all four publications.

All of these publications studied bisacodyl doses higher than the 14 mg dose that is predicted to produce the same amount of active metabolite as sodium picosulfate contained in the currently proposed dose of PrepoPik. In addition, these studies utilized additional means of cleansing the colon. They all utilized dietary changes of variable durations. Enemas were utilized in two (Rasmussen, et. al. and DiPalma, et. al.); in DiPalma, et. al. the bisacodyl was combined with a low magnesium citrate dose.

With regard to magnesium citrate, none of the studies utilized the magnesium citrate dose present in solution for PrepoPik. In two studies, the dose was exceeded, and in DiPalma, et. al., the dose used was less. In addition, other means of cleansing the colon were utilized. All studies utilized dietary changes of variable durations. Enemas were utilized in one (DiPalma, et. al.). In DiPalma, et. al., 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 citrate was combined with senna (the comparator arm was magnesium citrate only).

The lower bound of the 95% confidence intervals around the point estimate for proportion of responders treated with magnesium citrate was < 70% in all of the studies with the exception of Berkelhammer et al. and the magnesium plus senna arm in Vradelis, et al. However, these 2 studies utilized magnesium citrate doses that exceeded that derived from PrepoPik in solution, and the study arms in Vradelis et al. that had a more favorable outcome also exposed subjects to the stimulant laxative senna. Despite more "favorable" outcomes observed in these studies, their design and selected magnesium citrate dose provide no evidence that the use of magnesium citrate alone at the doses produced with PrepoPik would provide adequate colon cleansing in support of the ethical conduct of a full factorial study.

In conclusion, based on available evidence, a full factorial study to support PrepoPik approval where sodium picosulfate or magnesium citrate would be used as monotherapy would be unethical. There is sufficient evidence to suggest, based upon the above publications, that these components would be ineffective as monotherapy and that their use as monotherapy would place patients at risk of having inadequate bowel cleansing and therefore an inadequate colorectal screening at colonoscopy.

PEDIATRIC CONSIDERATIONS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric trials will be waived in patients from birth to 1 year because the product fails to show a meaningful benefit over existing therapies in this age group and is unlikely to be used in a substantial number of patients in this age group. (Bowel prep is achieved by administration of clear liquids for 24 hours in this age group).

Pediatric trials will be deferred in the 1 year (b) (4) age group since the application is ready for approval in adults at this time. Pediatric studies in the 1 year to 16 year old age range will be required post-marketing as follows:

- Study 1: Randomized, single blind, multicenter, dose ranging study with PK assessment comparing the safety and efficacy of PrepoPik to community standard of care in children ages 9 to 16 years undergoing elective colonoscopy. The primary efficacy endpoint will be the Aronchick Scale for efficacy (as it was for the adult population) and safety.

Subsequent to the analysis of Study 1, the following study will be conducted:

- Study 2: Randomized, single blind, multicenter, dose ranging study with PK assessment comparing the safety and efficacy of PrepoPik to community standard of care in children ages 2 years to < 9 years undergoing elective colonoscopy with safety and efficacy assessments as described for Study 1.

Subsequent to the analysis of Study 2, the following study will be conducted:

- Study 3: Randomized, single blind, multicenter, dose ranging study with PK assessment comparing the safety and efficacy of PrepoPik to community standard of care in children ages 1 year to < 2 years of age undergoing elective colonoscopy with safety and efficacy assessments as described for Study 2.

POSTMARKETING REQUIREMENTS and COMMITMENTS

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct post-marketing studies and clinical trials for certain purposes, if FDA makes certain findings required by statute.

FDA has determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk related to the potential for long term renal failure.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based upon appropriate scientific data the applicant will be required to conduct the following:

- A retrospective study to further evaluate fluid, electrolytes and kidney function in selected study patients.

TRADENAME REVIEW

Ferring Pharmaceuticals, Inc. submitted a request for review of the proposed proprietary name Picoprep on January 20, 2012. On April 26, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) found the proprietary name of Picoprep unacceptable because of orthographic similarity to both prescription and over the counter drugs.

The applicant submitted a request for the proposed proprietary name of Prepopik on May 23, 2012. On June 25, 2012, the proprietary name of Prepopik was found acceptable by DMEPA.

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/s/

VICTORIA KUSIAK
07/16/2012