CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-892

MEDICAL REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: March 16, 2006

FROM: Brian E. Harvey, M.D., Ph.D.
Division Director, DGP/ODE III/OND

SUBJECT: Division Director Concurrence Memo
NDA 21-892

APPLICANT: Salix Pharmaceutical Company, Inc

DRUG: OsmoPrep (Sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)

DATE SUBMITTED: May 17, 2005

DIVISION RECOMMENDATION:

The primary Medical Officer and Medical Team Leader both recommend that NDA 21-892, OsmoPrep, be approved for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older. I concur with these recommendations.

I. BACKGROUND:

For the indication of cleaning the colon prior to colonoscopy, there are two classes of bowel preparation products approved in the U.S.: the sodium phosphate-based and polyethylene glycol (PEG)-based products.

A previously approved product, sodium phosphate oral tablets (Visicol), is similar to OsmoPrep. However, OsmoPrep uses PEG 8000 as a binder and does not contain any microcrystalline cellulose (MCC). The Visicol formulation contains 13% MCC and the sponsor claimed that MCC occasionally obscures the appearance of the colonic mucosa during the colonoscopy procedure. This claim regarding MCC is supported by the published gastroenterology literature.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. DSI/DDMAC/DMETS:

The DDMAC and DMETS consultations were obtained for their perspectives on the proposed proprietary name. After rejecting the original trade name, a series of alternatives were submitted by the sponsor. One of these alternatives, "OsmoPrep" has been found to be acceptable by the clinical team and DMETS. In addition, DDMAC found "OsmoPrep" acceptable from a promotional perspective.

As reported by the Medical Team Leader, Dr. Khairy Malek, a clinical reviewer in the Division of Scientific Investigations (DSI), conducted the inspection in the three clinical sites and concluded that the violations observed in the first two sites (#12 and #31) did not adversely affect data acceptability and therefore the results of his inspection supported the use of this data in the NDA. The third site (# 3) did not have any reported violations, thus the data from that site are acceptable for use in support of this NDA. Dr. Malek did not indicate the need for follow-up inspections of these clinical sites.

B. CHEMISTRY AND MANUFACTURING:

The Chemistry Review Team has recommended approval and that OsmoPrep stability was acceptable up to 24 months. There are no outstanding chemistry issues based upon their review.

C. PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY:

The primary Pharmacology/Toxicology reviewer and team leader concluded that the NDA may be approved with the labeling changes which have now been finalized. The review team did not recommend that additional nonclinical studies be conducted. The Medical Team Leader noted that the sponsor authorized FDA to refer to NDA 21-097, Visicol® Tablets for additional nonclinical information. The review team did not report any unresolved nonclinical safety issues based upon their review of this data.

D. BIOPHARMACEUTICS:

As outlined by the Medical Team Leader, OsmoPrep is a reformulation of the previously approved Visicol® Tablets and has been submitted for the same indication for use. Therefore, no *in vivo* bioavailability studies were submitted in

this NDA and in the opinion of the Office of Clinical Pharmacology, this application met the *in vivo* bioavailability waiver provisions as stated in 21 CFR 320.22(b)(3).

E. CLINICAL:

Both the primary Medical Officer and the Medical Team Leader provided a detailed review and analysis of the clinical data submitted in support of this NDA. These reviews summarized the data as follows.

- Two efficacy trials were conducted. Studies II and III were randomized, investigator-blinded, active-controlled, parallel-group, multi-center studies in patients scheduled to have an elective colonoscopy.

- In Study III, patients were randomized 1:1:1 to receive 40 tablets of Visicol (60 grams of sodium phosphate); 40 tablets of OsmoPrep (60 grams of sodium phosphate); or 32 tablets of OsmoPrep (48 grams of sodium phosphate) by mouth

- In Study III, the pre-specified primary efficacy endpoint was the response rate to treatment. A responder was pre-specified as a patient who received an overall Colon Content Cleansing Score of excellent or good by a blinded colonoscopist on a 4-point Colonic Content Sale. A patient was considered a non-responder if their Overall Colon Cleansing Score was rated by the colonoscopist as fair or inadequate. In Study III, the statistical analysis was a non-inferiority analysis with a pre-specified 10% margin with appropriate multiplicity adjustments for the two comparisons (OsmoPrep 60 grams versus Visicol; OsmoPrep 48 grams versus Visicol).

- The data supported the conclusion that both the 60 and 48 gram OsmoPrep dosing regimens were non-inferior to the Visicol dosing regimen.

- In the safety database, no patients died; two patients experienced serious adverse events: one patient experienced ischemic colitis and the another patient experienced bloating and rectal bleeding. Seven patients discontinued study medication and of these seven drug-related discontinuations, five patients experienced nausea and/or vomiting and five patients experienced abdominal pain. The most common adverse events in the sodium phosphate treatment groups were abdominal distension, nausea, abdominal pain, and vomiting.

- The clinical team concluded that the safety profile for this drug was acceptable and that the proposed 48 gram OsmoPrep dosing regimen appeared to have an improved safety profile compared with the previously approved and currently marketed 60 gram Visicol regimen.

E. Pediatric Use:

The sponsor requested a full waiver for pediatric studies required under PREA. The review team recommended that the full waiver be granted, since this product:

- Did not represent a meaningful therapeutic benefit over the currently available products,
- Is not likely to be used in a substantial number of pediatric patients, and
- Most children would be unable/unwilling to swallow the number of large tablets necessary for adequate colon cleaning.

III. RECOMMENDATIONS FOR REGULATORY ACTIONS

I agree with the review team that NDA 21-892, OsmoPrep be approved for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older.

Initially, the clinical review team believed that as a post-marketing study commitment, the sponsor needed to conduct a thorough QT/QTc study of OsmoPrep in healthy subjects. After further discussion with the Clinical Pharmacology team and the sponsor, the primary Medical Officer and Medical Team Leader now believe that their concerns regarding electrolyte and cardiac abnormalities were not related to QTc issues, but were based upon altered electrolyte balances which could be identified by monitoring blood chemistry laboratory values. The review team now agrees that their concerns will be more appropriately addressed by requesting that the sponsor perform a Phase IV pharmacokinetic and safety study to assess the need for dose adjustment in patients with renal impairment. The sponsor has agreed to conduct this post-marketing study commitment as described in the approval letter dated March 16, 2006.

The sponsor requested a full waiver for pediatric studies required under the 2003 Pediatric Research Equity Act (PREA). I agree with the review team's recommendation that the full waiver be granted, and their justifications that this drug product does not represent a meaningful therapeutic benefit over the currently available products, is not likely to be used in a substantial number of pediatric patients, and that most children would be unable/unwilling to swallow the number of large tablets necessary for adequate colon cleaning.

IV. Labeling Recommendations:

The proposed changes to the product label have been outlined in both the primary Medical Officer review and the Medical Officer Team Leader memo. After discussions

with the sponsor and the review team, I concur with the negotiated label as attached to the approval letter dated March 16, 2005 for this NDA 21-892.

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/s/

Brian Harvey
3/16/2006 02:00:30 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 3/6/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-892

APPLICANT: InKine Pharmaceutical Company, Inc

DRUG: OsmoPrep (Sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)

RECOMMENDATION:

I concur with Dr. Eric Brodsky's recommendations that NDA 21-892, 48 gram OsmoPrep (sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP), be approved for cleansing of the large bowel as a preparation for colonoscopy in the adult population. For approval of this application, the sponsor needs to incorporate the Division's recommendations into the OsmoPrep drug label and agrees to the required post-marketing commitment studies.

As a post-marketing study commitment, the sponsor needs to conduct a thorough QT/QTc study of OsmoPrep in healthy subjects. In addition, the sponsor needs to perform a Phase IV study to assess the need for potential dose adjustment in subjects with renal impairment.

The sponsor requested a full waiver for pediatric studies required under the 2003 Pediatric Research Equity Act (PREA). I recommend that the full waiver be granted, because this drug product does not represent a meaningful therapeutic benefit over the currently available liquid purgative products and is not likely to be used in a substantial number of pediatric patients. In addition, most children would be unable, or at best very reluctant, to swallow the number of large tablets necessary for adequate purgation.

The sponsor submitted a report of an *in vitro* osmolarity study to examine the contribution of PEG 8000 to the osmotic activity of the OsmoPrep formulation. The results of this study indicated that the contribution of PEG-8000 to the osmotic activity of OsmoPrep was negligible.

The sponsor has authorized the Agency to refer to Visicol Tablet's NDA (NDA 21-097) approved on September 21, 2000 for the nonclinical information. There are no nonclinical safety issues remaining at this time. For more information, please see Dr. Tamal K. Chakraborti's review.

D. Biopharmaceutics:

OsmoPrep is a reformulation of Visicol® Tablets (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP. Moreover, the proposed indication for OsmoPrep is the same as for Visicol®. Compared to Visicol®, OsmoPrep has identical active ingredients but different excipients. No *in vivo* bioavailability studies were submitted in this NDA. It is the opinion of the Office of Clinical Pharmacology that this application meets the *in vivo* bioavailability waiver provisions of 21 CFR 320.22(b)(3). Please see Dr. Suliman Al-Fayoumi's review for details.

E. Clinical/Statistical:

Efficacy:

The two efficacy trials (Studies II and III) were randomized, investigator-blinded, active-controlled, parallel-group, multi-center (6 and 32 sites in Studies II and III, respectively), large bowel preparation U.S. trials in patients scheduled to have an elective colonoscopy. Study II, a phase 2 study, was intended to identify optimal doses for use in a subsequent phase 3 study (Study III).

In Study III, patients were randomized 1:1:1 to receive 40 tablets of Visicol (60 grams of sodium phosphate); 40 tablets of OsmoPrep (60 grams of sodium phosphate); or 32 tablets of OsmoPrep (48 grams of sodium phosphate) by mouth. These two dosing regimens were two of the best performing treatments in the phase 2 study (Study II).

In Study III, the pre-specified primary efficacy endpoint was the response rate to treatment. A responder was pre-specified as a patient who received an overall Colon Content Cleansing Score of excellent or good by a blinded colonoscopist on a 4-point Colonic Content Sale. A patient was considered a non-responder if their Overall Colon Cleansing Score was rated by the colonoscopist as fair or inadequate. In Study III, the statistical analysis was a non-inferiority analysis with a pre-specified 10% margin with

appropriate multiplicity adjustments for the two comparisons (OsmoPrep 60 grams versus Visicol and OsmoPrep 48 grams versus Visicol).

Table I summaries the efficacy results — the percentage of patients who were graded excellent, good, fair or inadequate on the Overall Colon Contents Cleansing Scale in Study III.

Table I: Summary of Efficacy Results in the all assessed population* in Study III

	Excellent N (%)	Good N (%)	Fair N (%)	Inadequate N (%)	Responder (excellent + good) N (%)	Difference in Responder Rate
Visicol 60g g(n=235)	120 (51)	102 (43)	13 (6)	0 (0)	222 (94.5)	
Osmoprep 60 grams (n=233)	170 (73)	56 (24)	5 (2)	2 (1)	226 (97.0)	2.5%**
Osmoprep 48 grams (n=236)	180 (76)	45 (19)	7 (3)	4 (2)	225 (95.3)	0.8%**

* All assessed population = Patients who ingested at least one sodium phophate tablet and had a colonoscopy.
** $p<0.0001$.

The study indicated that both the 60 and 48 gram OsmoPrep dosing regimens were non-inferior to the Visicol dosing regimen.

In summary, the clinical data from this well-controlled study support the efficacy of the sponsor's proposed 48 gram OsmoPrep dosing regimen for colon cleansing prior to a colonoscopy. For a detailed efficacy evaluation, please see Dr. Eric Brodsky's review.

Safety:

Of the 947 subjects/patients in the total safety population in this NDA (including the one phase 1 study, the one phase 2 trial, and the one phase 3 trial), 663 (70%), 268 (28%), and 16 (1.7%) subjects/patients received OsmoPrep, Visicol, and PEG 8000 respectively. Of the 663 patients who received OsmoPrep in the safety population, 599 (90%) patients received a dose that was equal or greater than the sponsor's proposed marketing total dose. The overwhelming majority of patients in the two colonoscopy trials were exposed to their bowel preparation for less than 24 hours. In the two colonoscopy trials, out of a total of 931 patients, 228 (24%) were 65 years old or older.

In the entire safety database, no patient died; two patients experienced serious adverse events: one patient experienced ischemic colitis and the another patient experienced bloating and rectal blooding. Both patients received the OsmoPrep 60 gram. There were no SAE in other treatment arms. Seven patients discontinued study medication (five and two patients received the 60 gram and the 48 gram OsmoPrep dosage regimen, respectively). Of the seven drug-related discontinuations, five patients experienced

nausea and/or vomiting and five patients experienced abdominal pain. The most common adverse events and the most common drug-related in the sodium phosphate treatment groups were abdominal distension, nausea, abdominal pain, and vomiting.

All three sodium phosphate treatment groups developed a high percentage of electrolyte abnormalities (including hyperphosphatemia, hypokalemia, hypocalcemia, and hypernatremia). In Study III, 96%, 96%, and 93% of patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep, respectively, developed hyperphosphatemia (defined as phosphate level > 5.1 mg/dL) and the mean phosphate levels of these three treatment groups were 7.6, 7.9, and 7.1 mg/dL, respectively, on the day of the colonoscopy. In Study III, 20%, 22%, and 18% of patients who took 60 grams of Visicol, 60 grams of Osmoprep, and 48 grams of Osmoprep developed hypokalemia (defined as a potassium level < 3.4 mEq/L), respectively. No patient clearly developed a serious AE or discontinued study medication due to an electrolyte disorder.

There was no thorough QT/QTc study performed.

In summary, the safety profile for this drug was acceptable. The sponsor's proposed 48 gram OsmoPrep dosing regimen appears to have an improved safety profile compared with the approved and marketed 60 gram Visicol regimen; therefore, the OsmoPrep safety program is adequate for approval of this NDA.

F. Pediatric Use:

The sponsor requested a full waiver for pediatric studies required under PREA. I recommend that the full waiver be granted, because this drug product does not represent a meaningful therapeutic benefit over the currently available liquid purgative products and is not likely to be used in a substantial number of pediatric patients.

II. Labeling Recommendations:

I concur with Dr. Eric Brodsky's labeling recommendations listed in his review. The labeling recommendations are summarized as following:

- For the CLINICAL STUDIES section,
  - delete the description for the phase II study;
  - add demographic data for the phase III study;
  - delete Tables 3, 4, and 5 (which contain the results of many secondary endpoints);
- Since sodium phosphate products have been associated with post-marketing cases of serious electrolyte disorders including seizures, cardiac arrhythmias, and renal failure (including acute phosphate nephropathy), these disorders will be included in the WARNINGS section;

- The CONTRAINDICATIONS section should not include diseases (including [redacted] that are unknown hazards. The WARNINGS section of the label should include these diseases;
- The PRECAUTIONS section should recommend that pre-dose and post-colonoscopy ECGs should be performed in patients with a known prolonged QT;
- The ADVERSE EVENTS section should include diarrhea as a common AE.

For a detailed labeling recommendations, please see Dr. Eric Brodsky's review.

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/s/

Ruyi He
3/6/2006 05:57:48 PM
MEDICAL OFFICER

CLINICAL NDA REVIEW TEMPLATE FOR OSMOPREP

Application Type	NDA
Submission Number	21-892
Submission Code	000
Letter Date	5/17/05
Stamp Date	5/17/05
PDUFA Goal Date	3/17/06
Reviewer Name	Eric Brodsky, MD
Review Completion Date	3/3/06
Established Name	Sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP
(Original Proposed) Trade Name	[redacted]™
(Approved) Trade Name	OsmoPrep™
Therapeutic Class	Purgative
Applicant	InKine Pharmaceutical Company, Inc
Priority Designation	Standard
Formulation	Oral tablet
Proposed Dosing Regimen	The evening before colonoscopy: 4 tablets every 15 minutes for a total of 20 tablets Three to five hours prior to colonoscopy: 4 tablets every 15 minutes for a total of 12 tablets
Proposed Indication	OsmoPrep™ Tablets are indicated for cleansing of the bowel as a preparation for colonoscopy, in adults 18 years of age or older.
Intended Population	Adults undergoing preparation for colonoscopy.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends **approval** of the 48 gram OsmoPrep™ (sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP) dose regimen for cleansing of the colon as a preparation for colonoscopy in adults ≥ 18 years of age if the sponsor agrees to important labeling changes and agrees to two phase IV commitments. If the sponsor does not agree to the important labeling changes and to the important phase IV commitment, then this medical officer recommends an **approvable** action.

Two well-controlled, randomized, investigator-blinded, parallel-group, multi-center, U.S. trials of OsmoPrep demonstrated substantial evidence of effectiveness and safety for the intended use of OsmoPrep as a colon preparation prior to a colonoscopy.

This medical officer recommends adding **WARNINGS** to the OsmoPrep label about the risk of serious adverse events and electrolyte changes after OsmoPrep administration in patients with the following risk factors: renal insufficiency, history of acute phosphate nephropathy, electrolyte disorders, seizures, and patients at increased risk of arrhythmias. Additionally, this medical officer recommends phase 4 commitments to conduct a thorough QT/QTc study of OsmoPrep in healthy subjects and a pharmacokinetic study of OsmoPrep in patients with renal insufficiency.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk Management Activities are not indicated.

1.2.2 Required Phase 4 Commitments

This medical officer recommends the sponsor perform a phase 4 commitment to conduct a thorough QT/QTc study of OsmoPrep in healthy subjects because the sponsor did not submit a thorough QT/QTc study in this NDA; the sponsor did not perform a thorough QT/QTc study for Visicol (under NDA 21-097); and did not conduct baseline or post-dose ECGs in their two OsmoPrep studies. Furthermore, there are several post-marketing reports of arrhythmias with sodium phosphate use and the serious electrolyte abnormalities associated with OsmoPrep use are known to increase the risk of arrhythmias. The sponsor should refer to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* for further guidance.

This medical officer recommends a second phase 4 commitment to conduct a pharmacokinetic study of OsmoPrep in patients with normal renal function and mild, moderate, and severe renal impairment. This medical officer recommends this study because many post-marketing serious

adverse events associated with sodium phosphate colon preparations have occurred in renal insufficiency patients.

1.2.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

InKine Pharmaceutical Company, Inc (InKine) submitted this new drug application [under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act] to support the approval of oral OsmoPrep™ (sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP) Tablets, an osmotic purgative, "for cleansing of the bowel as a preparation for colonoscopy, in adults 18 years of age or older" who are scheduled for an elective colonoscopy. OsmoPrep is a reformulation of Visicol® Tablets approved on September 21, 2000 (under NDA 21-097). The most important compositional change in OsmoPrep is that polyethylene glycol (PEG) 8000, the OsmoPrep binder, replaced microcrystalline cellulose, the insoluble blinder, in Visicol that occasionally obscured the visualization of the colon. The sponsor proposes to market a lower sodium phosphate dose containing 48 grams of sodium phosphate (the 48 gram OsmoPrep dosing regimen) compared to the 60 grams of sodium phosphate in the Visicol colon preparation regimen.

InKine submitted a total of three completed clinical studies to support the approval of their application. In the three trials, the entire safety database had a total population of 947 subjects/patients. Of the 947 subjects/patients, 663 (70.0%) and 268 (28.3%) patients received OsmoPrep and Visicol, respectively, and 16 (1.7%) subjects received PEG 8000.

The most important clinical trials — to support the efficacy and safety of OsmoPrep in colon cleansing before colonoscopy — included two trials of patients scheduled to receive an elective colonoscopy in the United States (Studies II and III). The two trials had a safety subpopulation of 931 patients [of which 663 (71.2%) and 268 (28.8%) patients received OsmoPrep and Visicol, respectively]. The overwhelming majority of patients in the two trials were exposed to their colon preparation (OsmoPrep or Visicol) for less than 24 hours.

1.3.2 Efficacy

The two most important efficacy trials (Studies II and III) were randomized, investigator-blinded, active-controlled, parallel-group, U.S., multi-center (6 and 32 sites in Studies II and III, respectively), colon preparation trials of OsmoPrep in patients scheduled to have an elective colonoscopy. Study II, a phase 2 study, was intended to identify optimal OsmoPrep doses for use in a subsequent phase 3 study (Study III).

In Study II, patients were randomized to one of seven sodium phosphate regimens including one Visicol regimen (Arm A) and six OsmoPrep regimens (Arms B, C, D, E, F, and G). The Visicol regimen was the approved dosage regimen containing 60 grams of sodium phosphate split between the day before the colonoscopy and the morning of the colonoscopy. The six OsmoPrep dosage regimens differed in the following ways:

1) OsmoPrep regimens B and C, D and E, and F and G contained 60, 48, and 42 grams of sodium phosphate, respectively;
2) Four OsmoPrep dosage regimens (B, C, E, and G) had split doses (on the day before the colonoscopy and on the day of the colonoscopy) and two OsmoPrep regimens (D and F) were administered only during the evening prior to the colonoscopy;
3) For each split dose, the length of time that patients were required to finish the bowel preparation varied from 0.25 to 1.5 hours; and
4) OsmoPrep regimens B, C, D and E, and F and G required 3.36, 2.4, 1.92, and 1.68 liters of clear fluid, respectively.

In Study III, patients were randomized 1:1:1 to receive 40 tablets of Visicol (60 grams of sodium phosphate); 40 tablets of OsmoPrep (60 grams of sodium phosphate); or 32 tablets of OsmoPrep (48 grams of sodium phosphate) by mouth. These two OsmoPrep dosing regimens were two of the best performing OsmoPrep treatments in the phase 2 study.

In Study III, the pre-specified **primary efficacy endpoint** was the response rate to treatment. A responder was pre-specified as a patient who received an overall Colon **Content** Cleansing Score of excellent (1) or good (2) by a blinded colonoscopist on a 4-point Colonic Content Sale (see Table i.). A patient was considered a non-responder if their Overall Colon Cleansing Score was rated by the colonoscopist as fair (3) or inadequate (4). In Study III, the statistical analysis was a non-inferiority analysis with a pre-specified 10% margin with appropriate multiplicity adjustments for the two comparisons (OsmoPrep 60 grams versus Visicol and OsmoPrep 48 grams versus Visicol).

Table i.: Four-point Colonic Content Scale

GRADE	#	DEFINITION
Excellent	1	>90% of mucosa seen, mostly liquid **colonic contents***, minimal suctioning needed for adequate visualization
Good	2	>90% of mucosa seen, mostly liquid **colonic contents***, significant suctioning needed for adequate visualization
Fair	3	>90% of mucosa seen, mixture of liquid and semisolid **colonic contents***, could be suctioned and/or washed
Inadequate	4	<90% of mucosa seen, mixture of semisolid and solid **colonic contents*** which could not be suctioned or washed

* Colonic contents were defined as all liquid, semisolid, and solid material in the lumen of the colon
Reference: Section 9.5.4.1, Page 27

In Study II, the pre-specified **co-primary efficacy endpoints** were the following:

1) Overall quality of Colon **Content** Cleansing (identical to the primary efficacy endpoint in Study III); and
2) Overall quality of Colon **Stool** Cleansing: A patient was considered to be a responder if Overall Colon Cleansing was rated by the blinded colonoscopist as excellent (1) or good (2) according to a 4-point Colonic Stool Scale. The Stool Scale was identical to the Content Scale except for the following difference: in the Stool Scale, a colonoscopist judged the quality of the preparation based on only stool; whereas, in the Content Scale a colonoscopist judged the quality of the preparation based on all colon contents including stool and all liquid, semisolid, and solid material in the colon lumen.

Of the 16 pre-specified secondary efficacy endpoints in Study III, this medical officer believes the following were the three most **important secondary endpoints**:

1) Mean Overall Colon Content Cleansing Score;
2) Ascending colon cleansing response rate (excellent or good); and
3) Mean ascending colon content cleansing score.

Since Study II was a dose ranging study (six comparisons) without multiplicity adjustments, Study II's secondary endpoints were not evaluated by this medical officer.

Since this medical officer believes that the 4-point Overall Colon Content Scale contained overlapping Likert responses [the good (2) and fair (3) responses overlap], this medical officer analyzed the following two **exploratory efficacy responder endpoints** that did not contain overlapping responses:

1) Responders are patients who were given an excellent (1) score and non-responders are patients who received a good (2), fair (3), or inadequate (4) score on the 4-point Colon Content Scale; and
2) Responders are patients who were given an excellent (1), good (2), or fair (3) score and non-responders were patients who received an inadequate (4) score on the 4-point Colon Content Grading Scale.

Primary Efficacy Endpoint Results: Table ii displays the results of only one of the two co-primary efficacy endpoints — the percentage of patients who were graded excellent (1) or good (2) on the 4-point Overall Colon Contents Cleansing Scale — since the results of both co-primary efficacy endpoints were very similar in Study II. Since the OsmoPrep 60 gram split dose (Arm C) and the OsmoPrep 48 gram split dose (Arm E) were two of the best responders, they were selected for the two OsmoPrep dosing regimens in Study III.

Table ii: Patients with excellent (1) or good (2) Overall Colon Content Cleansing in the AAP* in Study II

	Visicol 60 g Arm A	OsmoPrep 60 g Split dose (3 pills) Arm B	OsmoPrep 60 g Split dose (4 pills) Arm C	OsmoPrep 48 g PM-only Arm D	OsmoPrep 48 g Split dose Arm E	OsmoPrep 42 g PM-only Arm F	OsmoPrep 42 g Split dose Arm G	All Treatments (n=214)
n	29	32	29	30	33	32	29	214
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	25 (86)	31 (97)	29 (100)	27 (90)	32 (97)	23 (72)	26 (90)	193 (90)
Non-responder	4 (14)	1 (3)	0 (0)	3 (10)	1 (3)	9 (28)	3 (10)	21 (10)

* AAP = All Assessed Population (patients who ingested at least one sodium phophate tablet and had a colonoscopy); Visicol was compared to six OsmoPrep groups.
Reference: Final Report Study II, Section 11.1, Table 11.1-1, Page 45.

Table iii delineates the primary efficacy results — the percentage of patients who were graded excellent (1) or good (2) on the 4-point Overall Colon Contents Cleansing Scale — in Study III. Both the 60 and 48 gram OsmoPrep dosing regimens demonstrated non-inferiority compared to the Visicol dosing regimen.

Table iii: Patients with excellent (1) or good (2) Overall Colon Content Cleansing in the AAP* in Study III

	Responder n (%)	Non-Responder n (%)	Difference in Response Rate	Lower bound of the one-sided 97.5% confidence interval** % (p-value)
Visicol 60 grams (n=235)	222 (94.5)	13 (5.5)		
OsmoPrep 60 grams (n=233)	226 (97.0)	7 (3.0)	2.5%	-1.0% (< 0.0001)
OsmoPrep 48 grams (n=236)	225 (95.3)	11 (4.7)	0.8%	-2.8% (< 0.0001)

* AAP = all assessed population (patients who ingested at least one sodium phophate tablet and had a colonoscopy).
** The pre-specified non-inferiority margin was 10%.
Reference: Final Report Study III, Section 11.1, Table 11.1-1, Page 56.

Important Secondary Endpoints and FDA Post-hoc Responder Analyses in Study III: All three important secondary endpoints in Study III demonstrated that both OsmoPrep dosing regimens were numerically superior to the Visicol dosing regimen. Furthermore, in the two FDA post-hoc efficacy responder analyses, both OsmoPrep dosing regimens were numerically superior or non-inferior to the Visicol dosing regimen.

In summary, the clinical data from the two well-controlled OsmoPrep studies support the efficacy of the sponsor's proposed 48 gram OsmoPrep dosing regimen for colon cleansing prior to a colonoscopy.

1.3.3 Safety

Of the 947 subjects/patients in the total safety population in this NDA (including the one phase 1 study, the one phase 2 trial, and the one phase 3 trial), 663 (70%), 268 (28%), and 16 (1.7%) subjects/patients received OsmoPrep, Visicol, and PEG 8000 respectively. Of the 663 patients who received OsmoPrep in the safety population, 599 (90%) patients received an OsmoPrep dose that was equal or greater than the sponsor's proposed marketing OsmoPrep dose. The overwhelming majority of patients in the two colonoscopy trials were exposed to their bowel preparation (OsmoPrep or Visicol) for less than 24 hours. In the two colonoscopy trials, out of a total of 931 patients, 228 (24%) were 65 years old or older.

In the entire safety database, no patient died; two patients experienced serious adverse events (both patients received the OsmoPrep 60 gram dosage regimen); and seven patients experienced drug-related discontinuation of study medication (five and two patients received the 60 gram and the 42 gram OsmoPrep dosage regimen, respectively). Of the two patients who experienced serious adverse events, one patient developed abdominal cramping, symptomatic postural hypotension, hypokalemia, and ischemic colitis and one patient developed severe bloating, rectal bleeding, and ileus. Of the seven drug-related discontinuations, five patients experienced nausea and/or vomiting and five patients experienced abdominal pain. The most common adverse events and the most common drug-related adverse events in the sodium phosphate treatment groups were abdominal distension, nausea, abdominal pain, and vomiting. The dose regimens containing the greatest amounts of sodium phosphate (the 60 gram OsmoPrep and the 60 gram Visicol dosage regimens) had higher frequencies of common adverse events and drug-related common adverse events compared to the 48 gram OsmoPrep dosage regimen.

All three sodium phosphate treatment groups developed a high percentage of electrolyte abnormalities (including hyperphosphatemia, hypokalemia, hypocalcemia, and hypernatremia). In Study III, 96%, 96%, and 93% of patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep, respectively, developed hyperphosphatemia (defined as phosphate level > 5.1 mg/dL) and the mean phosphate levels of these three treatment groups were 7.6, 7.9, and 7.1 mg/dL, respectively, on the day of the colonoscopy. In Study III, 20%, 22%, and 18% of patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep developed hypokalemia (defined as a potassium level < 3.4 mEq/L), respectively. No patient clearly developed a serious adverse event or discontinued study medication due to an electrolyte disorder.

Given the known rare, post-marketing electrolyte abnormalities associated with serious adverse events (including renal failure, acute phosphate nephropathy, seizures, and arrhythmias) after sodium phosphate administration, the following are the major deficiencies of the OsmoPrep safety monitoring program in Studies II and III:

1) Lack of any post-colonoscopy blood tests;
2) Lack of any post-colonoscopy follow-up safety visits;
3) Lack of any screening, treatment period, or post-treatment period ECGs performed;
4) No thorough QT/QTc study performed; and
5) Lack of information on the safety and efficacy of OsmoPrep in renal insufficiency patients.

Since the OsmoPrep clinical studies excluded a wide range of patient disorders (renal insufficiency; known or suspected electrolyte disorders; untreated dysrhythmias; gastrointestinal, heart, or liver disease of any kind; ascites; recent acute gastroenteritis; recent laxative use; and/or recent constipation), extrapolation of the OsmoPrep safety database to other populations is limited.

This medical officer believes that the sponsor's safety database exposure was acceptable. In addition, the sponsor's proposed 48 gram OsmoPrep dosing regimen appears to have an improved safety profile compared with the approved and marketed 60 gram Visicol regimen; therefore, this medical officer believes that the OsmoPrep safety program will be adequate for approval if the following two conditions are met by the sponsor:

1) Labeling changes are made to reflect the above deficiencies in the OsmoPrep safety program; and
2) A commitment is made to perform phase 4 post-marketing study commitments to conduct a thorough QT/QTc study in healthy subjects and a pharmacokinetic study in patients with renal insufficiency.

1.3.4 Dosing Regimen and Administration

This medical agrees with the sponsor's proposed 48 gram OsmoPrep dose regimen (with a total of 2 quarts of clear fluid) for adults with the following instructions:

- The night before the colonoscopy: (——— , take 4 OsmoPrep tablets at a time with 8 ounces of clear liquid every 15 minutes (———) for a total of 20 tablets (30 grams);
- The day of the colonoscopy: Starting 3 to 5 hours prior to the colonoscopy, take 4 OsmoPrep tablets ——— with 8 ounces of clear liquid every 15 minutes (———) for a total of 12 tablets (18 grams).

1.3.5 Drug-Drug Interactions

There are no important drug-drug interactions.

1.3.6 Special Populations

There are no special OsmoPrep dosing considerations for gender, race, age, and patients with hepatic insufficiency.

Since there have been post-marketing reports of renal failure associated with sodium phosphate bowel preparation use and there is no OsmoPrep safety information in patients with renal insufficiency, this medical officer recommends that renal insufficiency patients should have pre-dosing and post-colonoscopy blood tests (including phosphate, calcium, potassium, sodium, BUN, and creatinine). Similarly, severe hepatic insufficiency patients should have these lab tests pre-dosing and post-colonoscopy because of the increased risk of electrolyte disorders in this population.

This medical officer agrees with the sponsor's request for a full waiver for pediatric studies that are required under the 2003 Pediatric Research Equity Act. This medical officer believes that the sponsor has demonstrated that pediatric studies are not necessary under 21 CFR 314.55(c)(2)(i) where a full waiver can be granted if the "drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients."

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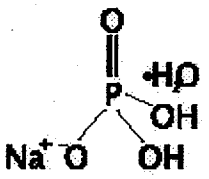
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

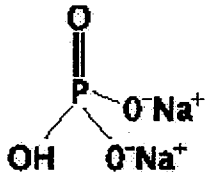
Proposed Trade Name (established name): OsmoPrep™ (sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP)

The structure, molecular formula, and molecular weights of the two active ingredients of OsmoPrep (sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous) are shown below.

- Sodium phosphate monobasic monohydrate, USP, has a molecular formula of $NaH_2PO_4 \cdot H_2O$; a molecular weight of 137.99; and the following structure:



- Sodium phosphate dibasic anhydrous, USP has a molecular formula of Na_2HPO_4; a molecular weight of 141.96; and the following structure:



Proposed Indication: Cleansing of the bowel as a preparation for colonoscopy, in adults 18 years of age or older.

Proposed Age Group: Adults

Pharmacologic Class: Osmotic purgative

Chemical Name: Sodium phosphate monobasic monohydrate, USP, and Sodium phosphate dibasic anhydrous, USP

Route of Administration, Description, and Formulation: Oral tablets are white to off-white.

Proposed Treatment Regimen: The evening before the colonoscopy, every 15 minutes take 4 OsmoPrep tablets with 8 ounces (240 mL) of clear liquid for five doses (20 OsmoPrep tablets) over one hour. The day of the colonoscopy (starting 3-5 hours before the colonoscopy), every 15 minutes

take 4 OsmoPrep tablets with 8 ounces (240 mL) of clear liquid for three doses (12 OsmoPrep tablets) over 30 minutes. Each OsmoPrep tablet contains 1.5 grams of sodium phosphate. Thus, the entire preparation has 32 tablets of OsmoPrep (containing 48 grams of sodium phosphate) with 64 ounces (1.92 Liters) of clear liquid.

Molecular Formula: $NaH_2PO_4 \cdot H_20$ (sodium phosphate monobasic monohydrate) and Na_2HPO_4 (sodium phosphate dibasic anhydrous)

2.2 Currently Available Treatment for Indications

There are two classes of bowel preparation products approved in the United States: sodium phosphate-based products and polyethylene glycol (PEG)-based products (see Table 1).

Approved sodium phosphate products include oral sodium phosphate solutions (OSPS) — which are marketed as professionally labeled products and sold over-the-counter (OTC) under the monograph system — and sodium phosphate oral tablets (Visicol). OsmoPrep is an oral sodium phosphate tablet product that is similar to Visicol, except that OsmoPrep does not contain any microcrystalline cellulose (MCC). The currently approved Visicol formulation contains 13% MCC. OsmoPrep uses PEG 8000 as a binder, instead of MCC. The sponsor claims that MCC occasionally obscures the appearance of the colon during colonoscopy and PEG 8000 will not obscure the colonic lumen.

Approved PEG-based products include GoLYTELY, Colyte, OCL Solution, NuLYTELY, and Tri Lyte. HalfLytely is a combination product containing 2 liters of a PEG-based oral solution and 20 mg of oral bisacodyl tablets (a stimulant laxative).

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Table 1: Approved prescription and OTC colon preparation products in the United States

Drug	NDA#	Sponsor	Approval Date	Ingredients	Fluid
GoLYTELY	19-011	Braintree	7/84	PEG 3350 + Electrolytes	Up to 4 liters
Colyte	18-983	Schwarz Pharma	10/84	PEG 3350 + Electrolytes	Up to 4 liters
Oral Sodium Phosphate Solution	N/A[1]	Multiple	N/A[1]	Sodium Phosphate (30 grams)	Varies[2]
OCL Solution[3]	19-284	Hospira	4/86	PEG 3350 + Electrolytes	Up to 4 liters
NuLYTELY	19-797	Braintree	4/91	PEG 3350 + Electrolytes	Up to 4 liters
Visicol	21-097	Inkine	9/00	Sodium Phosphate (60 grams)	3.4 liters
HalfLytely Bisacodyl Kit	21-551	Braintree	5/04	PEG 3350, Electrolytes, + Bisacodyl	2 liters
Tri Lyte	N/A[4]	Schwarz Pharma	2/04	PEG 3350 + Electrolytes	Up to 4 liters
MOVIPREP	21-881	Norgine BV	**Not Approved; Under Review**	PEG 3350, Electrolytes, + Vitamin C	2 liters
OsmoPrep	21-892	Inkine	**Not Approved; Under Review**	Sodium Phosphate (48 grams) + PEG 8000	1.9 liters

1 Oral Sodium Phosphate Solutions (OSPS) are not under NDA regulations; rather they are approved under OTC monograph regulations. The tentative final monograph was proposed in 1985. The Final Rule has not been completed. OSPS are professionally labeled and marketed OTC.
2 The Final Rule for the professionally labeled bowel preparations sold OTC has not been completed. Manufacturers recommend different amounts of concomitant fluid intake for their bowel preparation products.
3 OCL Solution has been discontinued and is not marketed in the United States.
4 Tri Lyte is a generic product (identical to NuLYTELY) approved under ANDA76-491.
Reference: Adapted from current product labels and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

In addition to the FDA-approved sodium phosphate-based and PEG-based bowel preparations, many laxatives are prescribed off-label for bowel cleansing for colonoscopy, surgery, and radiologic examinations (such as barium enemas). Additionally, physicians use several unapproved dose regimens of sodium phosphate-based and PEG-based bowel preparation products. Additionally, physicians recommend various amounts of concomitant fluid intake during administration of bowel preparations.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in OsmoPrep is sodium phosphate. The following two formulations of sodium phosphate products are approved for bowel preparation: OSPS, which are marketed as professionally labeled products and sold OTC under the monograph system, and sodium phosphate oral tablets (Visicol). In addition, OSPS are approved as laxatives for the treatment of occasional constipation and they are sold OTC. Under the tentative final monograph, the dosage of OSPS for occasional constipation (30 grams of sodium phosphate in a 24 hour period) is about half the dosage

of OSPS for bowel preparation (59 grams of sodium phosphate in a 24 hour period prior to colonoscopy).

The highlights of the regulatory activity of Visicol in the United States include the following:

- On September 21, 2000, Visicol was approved for "the cleansing of the bowel as a preparation for colonoscopy, in adults 18 years of age or older" by the Division of Gastroenterology Products (DGP).
- On March 12, 2002, after review of a chemistry supplement, the DGP approved a change in the Visicol formulation. The new Visicol formulation reduced the percentage of MCC in the drug product from 23% by weight to 13% by weight. According to the sponsor, the greater MCC content in the original Visicol formulation obscured the visualization of the colonic mucosa during colonoscopy. According to the sponsor, the lower MCC content in the new Visicol formulation would improve the visualization of the colon during colonoscopy.
- On February 10, 2005, the DGP approved a labeling supplement for Visicol to add information about Visicol-associated seizures to the **PRECAUTIONS** section of the label. The **PRECAUTIONS** section in the Visicol label was revised to include the following paragraph:

  "There have been reports of generalized tonic-clonic seizures and/or loss of consciousness associated with VISICOL® use in patients with no prior history of seizures. Cases of seizure were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypochloremia, hypocalcemia, hypomagnesemia) and low serum osmolality. Neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities. Other purgatives, including sodium phosphates solution and PEG-3350 containing products, have also been associated with seizures and alterations of consciousness in patients with and without a prior history of seizures. VISICOL® should be used with caution in patients with risk factors for hyponatremia, e.g., SIADH, a history of electrolyte abnormalities, inadequately treated hypothyroidism, use of other drugs associated with hyponatremia, e.g., thiazide diuretics, or adrenal insufficiency, or with risk factors for development of tonic-clonic seizures, e.g., a history of seizures, use of drugs that lower the seizure threshold such as tricyclic antidepressants, or withdrawal from alcohol or benzodiazepines."

- On September 26, 2005, the sponsor of Visicol submitted a Changes Being Effected labeling supplement that included the addition of **PRECAUTIONS** regarding sodium phosphate-associated acute renal failure and nephrocalcinosis. The sponsor amended the first paragraph in the **General** subsection in the **PRECAUTIONS** section in the Visicol label to the following:

  "Patients should be instructed to drink 8 ounces of clear liquids with each dose of VISICOL® Tablets (see Dosage and Administration). Inadequate fluid intake, as with any effective purgative, may lead to excessive fluid loss, possibly producing dehydration and hypovolemia. Dehydration from purgation may be exacerbated by inadequate oral fluid intake, nausea, vomiting, loss of appetite, or use of diuretic drugs, and may be associated with acute renal failure. There have been rare reports of acute renal failure with purgatives, including VISICOL®, sodium phosphate solution, and PEG-3350. There have also been

rare reports of nephrocalcinosis with sodium phosphate purgatives. Patients with conditions that may predispose to dehydration or those taking medications which may decrease glomerular filtration rate, such as angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), should be assessed for hydration status prior to use of purgative preparations and managed appropriately."

2.4 Important Issues With Pharmacologically Related Products

In February 2005, the DGP approved Visicol labeling supplement added safety information to the PRECAUTIONS section about post-marketing seizures associated with sodium phosphate administration.

In May 2005, Dr. Glen S. Markowitz, a renal pathologist at the Columbia College of Physicians and Surgeons medical center, gave a lecture entitled "Acute Phosphate Nephropathy Following Oral Sodium Phosphate Bowel Purgative: An Under-recognized Cause of Chronic Renal Failure" at the FDA. Subsequently, an internal working group was formed to evaluate serious complications of electrolyte abnormalities associated with bowel preparations (such as renal failure, seizures, and arrhythmias).

This medical officer from the DGP, Ann Corken Mackey, RPh, MPH, from the Division of Drug Risk Evaluation (DDRE) in the Office of Drug Safety (ODS), and Dr. Karen Feibus from the Office of Nonprescription Products (ONP) were the members of this working group. The working group evaluated a possible association of serious complications of electrolyte abnormalities and approved prescription and OTC bowel preparation products. The working group evaluated randomized, well-controlled bowel preparation studies submitted to the FDA; post-marketing adverse event (AE) reports; and the literature. On November 15, 2005, the working group presented the following post-marketing information to the Deputy Director of DGP, the office director of ONP, the division director of DDRE, a nephrology medical officer from the Division of Cardio-Renal Drug Products, and other members:

- Dr. Glen Markowitz identified 21 cases of renal biopsy-proven acute phosphate nephropathy and renal failure associated with the administration of sodium phosphate products prior to colonoscopy.
- According to the Adverse Event Reporting System (AERS), 5 fatalities, 4 nonfatal seizures, one renal failure, and 1 ventricular fibrillation case were reported in patients using PEG-based products as bowel preparations between 1996 and 2003.

  - In four of the five fatalities, the patients had underlying medical conditions including chronic renal insufficiency, megacolon, history of bowel perforation, and ascites.
  - The patient who developed renal failure had underlying end stage liver failure and was taken a concomitant diuretic.
  - The patient who developed a ventricular arrhythmia developed hypokalemia. This patient was successfully cardioverted.
  - All four patients who developed nonfatal seizures developed hyponatremia, were hospitalized, and then recovered.

- According to the AERS, 11 fatalities, 33 renal failure, 2 seizure, and 12 serious cardiac event cases were reported in patients using OSPS as a bowel preparation between 1969 and 2005 (not mutually exclusive). Since OSPS are under the monograph system and manufacturers of OSPS products are not required to report AEs, the AERS cases is most likely not the complete list of SAEs associated with OSPS. Most of these patients experienced clinically significant changes in electrolytes.

  - Of the 11 fatalities, 2 were cardiac arrests with higher doses of OSPS, 2 were cardiac arrests with recommended OSPS doses, 2 were patients with baseline renal insufficiency and the patients were given higher OSPS doses, and 1 patient developed a seizure and aspiration pneumonia who took a higher OSPS dose.
  - Of the 33 patients who developed renal failure associated with OSPS administration, 21 were over 65 years old. Of the 33 patients, 10 were male and 23 were female. Of the 33 patients, 22 had hypertension, 7 had type II diabetes, 4 had baseline renal insufficiency, 15 took an ACE inhibitor or ARB, 4 took a NSAID, and 7 took a diuretic. Also of the 33 patients, 5 patients received high OSPS doses. Acute renal failure onset was two days to about two months. Of the 33 patients, 4 developed end stage renal failure, at least 22 developed permanent chronic renal failure, at least 9 were hospitalized, and 7 required dialysis (outcomes were not mutually exclusive).
  - Of the 12 cases of serious cardiac events, 7 patients had cardiac arrest (5 of the 7 were fatal) and 5 patients had QT prolongation. Most of the patients with cardiac events had electrolyte abnormalities.

- According to the AERS, 1 fatality, 11 renal failure, 10 seizures, and 1 QT prolongation cases were reported in patients using Visicol as bowel preparations between 2001 and 2005. Most of these patients experienced significant changes in their electrolytes.

  - Of the 11 renal failure cases, 7 patients had hyperphosphatemia, 6 patients had hypocalcemia, 5 patients were over 65 years old, 7 patients were female and 5 patients were male, 10 had a history of hypertension, 4 had a history of diabetes type II, 2 had a history of chronic renal insufficiency, 9 were taking an ACE inhibitor or ARB, 6 were taking a NSAID, and 3 were taking a diuretic(not mutually exclusive). Of the 11 cases, 10 were hospitalized for renal failure and 2 required dialysis (not mutually exclusive).
  - Of the 10 patients who experienced a seizure, 10 patients developed hyponatremia, 8 had hypokalemia, and 7 had hypocalcemia. The seizure onset was between 2 to 16 hours after initiation of Visicol. Of the 10 patients, 1 had a history of a seizure disorder and 9 had no history of seizures.

2.5 Presubmission Regulatory Activity

The highlights of the regulatory activity of OsmoPrep in the United States include the following:

- In June 2004, InKine, the sponsor of OsmoPrep, submitted a request for a Special Protocol Assessment (SPA) of their proposed phase 3 protocol. On July 19, 2004, Dr. Joyce Korvick,

the deputy director of the DGP, accepted the sponsor's proposed phase 3 protocol and Dr. Korvick had the following comments:

- "Yes, we agree with your choice" of colon cleansing scale.
- The sponsor's proposal to define responders as patients who achieve an excellent or good grade on the colon cleansing scale is acceptable for the primary efficacy analysis.
- The sponsor's proposal to have a non-inferiority statistical analysis with an absolute 10% margin for the primary efficacy endpoint is acceptable.
- The sponsor's "proposed approach is acceptable" regarding their proposed safety monitoring in the phase 3 study.
- There "may be bias in the results (of the phase 3 study) if you use the phase 2 sites for the phase 3 study, since the investigators may be aware of (the) phase 2 results."

➢ On August 23, 2004, the DGP had an OsmoPrep end of phase 2 meeting with InKine and the DGP had the following comments:

- The sponsor's completed phase 2 study "could be supportive of a single phase 3 study, as long as the single phase 3 study is appropriately designed, includes the approved Visicol" dosage "regimen as (a) control, and ... show(s) significant efficacy in (the) non-inferiority analyses."
- "A waiver for pediatric studies may be acceptable; however, you should submit a formal request."
- In vivo "studies in healthy volunteers should be performed to determine the potential osmotic activity of PEG 8000." According to the sponsor, in this end of phase 2 meeting, the DGP raised a question regarding whether PEG 8000, the binder material used to replace MCC, contributed to the purgative effect of OsmoPrep, and the DGP recommended that the sponsor conduct a small clinical study to answer that question.
- If the sponsor intends "to pursue the NDA as a 505(b)(1) application, then you will need to perform the requested (non-clinical) studies. However, if you plan to pursue a 505(b)(2) application, then these non-clinical studies will not be necessary." The requested studies included 4-week toxicology studies in rodents and non-rodents species.

➢ On December 20, 2004, according to InKine, Dr. Joyce Korvick had a telephone conversation with Dr. Martin Rose, a representative from InKine. According to InKine, Dr. Korvick acknowledged the sponsor's concern regarding how to design a clinical study to evaluate if MCC contributed to the purgative effect of OsmoPrep. According to the sponsor, Dr. Korvick stated that the sponsor only needed to perform a small study in five or six healthy subjects to show that PEG 8000 does not provide a substantial contribution to the effects of OsmoPrep. Dr. Korvick stated that if the study showed no substantial contribution, then OsmoPrep would not be considered a combination product, toxicity studies would not be required, and the application could be submitted under 505(b)(2) of the Federal Food, Drug and Cosmetic Act.

- On March 10, 2005, the DGP had an OsmoPrep pre-NDA meeting with InKine and the DGP had the following comments:

  - "If PEG 8000 shows activity as an active ingredient" in the phase 1 clinical study, then "toxicology studies would still be needed."
  - "If PEG 8000 is an active ingredient, (then) the manufacturing site(s) for PEG 8000 should be ready for inspection at the time of NDA submission and CMC information for PEG 8000 would need to be submitted or cross-referenced to a DMF."

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dr. Roswitha Kelly stated that OsmoPrep's stability was acceptable up to 24 months. For more information see her review.

3.2 Animal Pharmacology/Toxicology

The sponsor submitted the results of one *in vitro* study examining the contribution of PEG 8000 to the osmotic activity of OsmoPrep (Study TRD-00064) and referred to their nonclinical program in the Visicol NDA (NDA 21-097). According to Dr. Tamal Chakroborti, the pharmacology/toxicology reviewer, the "results of this study indicated that the contribution of PEG-8000 to the osmotic activity of OsmoPrep was negligible." For more information, please see his review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Three sponsor-conduced trials (Studies I, II, and III) were evaluated by this medical officer for this review. Studies II and III were the randomized, investigator-blinded, actively-controlled, parallel-group, multi-center, U.S. studies of OsmoPrep in patients who were to receive an elective colonoscopy. All of the study reports were submitted electronically.

Since this investigational product is not marketed anywhere in the world, foreign post-marketing reports are not part of the sources of information for this review. However, for this review, this medical officer reviewed clinical studies of approved sodium phosphate products (including three adequate and well-controlled Visicol trials in NDA 21-097 and an oral sodium phosphate solution

trial) that were submitted to the FDA and post-marketing safety reports of serious adverse events (SAEs) associated with sodium phosphate preparations. This medical officer also consulted with Ann Corken Mackey, (a safety reviewer from DDRE) regarding the sodium phosphate post-marketing reports.

4.2 Tables of Clinical Studies

Table 2 displays the three clinical trials submitted in the OsmoPrep NDA. The two most important trials for the efficacy and safety review of this NDA are Studies II and III.

Table 2: A Summary of all the studies submitted in this NDA

Study	Design	Treatment Groups	N*
Study I (102-04-02)	**Phase 1**, R, DB, SC, U.S. cross-over study to compare the purgative effect of PEG-8000 with an inactive vehicle in healthy male subjects	1) Period 1: PEG 8000 and inactive vehicle Period 2: Inactive vehicle 2) Period 1: Inactive vehicle Period 2: PEG 8000 and inactive vehicle	16
Study II (102-03-01)	**Phase 2**, R, investigator-blinded (open label to patient), MC, U.S. study in adult patients scheduled for an elective colonoscopy	1) **Visicol** 60 grams (split doses – 30 grams in evening and 30 grams on day of colonoscopy) 2) **OsmoPrep** 60 grams (split doses – 30 grams over 1.5 hours in evening and 30 grams over 1.5 hours on day of colonoscopy) 3) **OsmoPrep** 60 grams (split doses – 30 grams over 1 hour in evening and 30 grams over 1 hour on day of colonoscopy) 4) **OsmoPrep** 48 grams (PM-only doses – 30 grams and then 18 grams in evening before colonoscopy) **5) OsmoPrep 48 grams (split doses – 30 grams in evening and 18 grams on day of colonoscopy)**** 6) **OsmoPrep** 42 grams (PM-only doses – 30 grams and then 12 grams in evening before colonoscopy) 7) **OsmoPrep** 42 grams (split doses – 30 grams in evening and 12 grams on day of colonoscopy)	30 32 29 30 **33** 33 31
Study III (102-04-01)	**Phase 3**, R, investigator-blinded (open label to patient), MC, U.S. study in adult patients scheduled for an elective colonoscopy	1) **Visicol** 60 grams (split doses – 30 grams in evening and 30 grams on day of colonoscopy) 2) **OsmoPrep** 60 grams (split doses – 30 grams in evening and 30 grams on day of colonoscopy) **3) OsmoPrep 48 grams (split doses – 30 grams in evening and 18 grams on day of colonoscopy)****	238 236 **239**

* The safety population; R = randomized; DB = double-blind, SC = single center; MC = multicenter
** This OsmoPrep dosage regimen is the sponsor's proposed marketing OsmoPrep dosing regimen
Reference: Adapted from ISS, Table 1, Pages 14-16

4.3 Review Strategy

This medical officer is responsible for the entire safety and efficacy reviews for the bowel preparation indication.

All three studies in this NDA (Studies I, II, and III) were reviewed in detail.

Studies II and III were evaluated for the efficacy and safety review because both trials contained the sponsor's proposed OsmoPrep dosing regimen, contained the proposed population (patients scheduled for an elective colonoscopy), included the FDA-approved Visicol dosing regimen as an active control, had similar designs, had similar efficacy endpoints, and had similar safety evaluations.

Study I was not included in the efficacy review for the following reasons:

- It did not contain any OsmoPrep or sodium phosphate treatment groups;
- It did not include the proposed population; rather, it included healthy male volunteers;
- It did not involve colonoscopy preparation;
- It was a small pharmacodynamic study to answer a specific question if PEG 8000 had a laxative effect.

4.4 Data Quality and Integrity

Three sites in Study III were selected for Division of Scientific Investigation (DSI) to conduct audits (see Table 3). These three Study III locations were selected because they had the largest number of patients per location. Sites 31, 12, and 3 included 71, 59, and 54 randomized patients, respectively. In comparison, the mean number of randomized patients per site in Study III was 26.

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Table 3: DSI-selected sites in Study III

Study	Site #	Investigator	Name and Location	N/n	DSI Audit Violations
Study III	31	Dr. Howard Schwartz	Miami Research Associates 7500 SW 87th Ave, Suite 200/202 Miami, FL 33173	71/63	1) Inclusion of a patient who should have been excluded 2) Failure to report an AE
Study III	12	Dr. Michael Goldstein	Long Island Gastrointestinal Research 310 E Shore Road, Suite 206 Great Neck, NY 11023	59/46	Incomplete physical exams on six patients
Study III	3	Dr. Nav Grandhi	Gastroenterology Research Consultants of Greater Cincinnati 10600 Montgomery Road, Suite 100 Cincinnati, OH 45242	54/46	None

N = the number of patients who were randomized in the study
n = the number of patients who completed the study
Reference: DSI reports by Ni Aye Khin

The DSI inspections were part of FDA's Bio-research Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

On October 17, 2005, Mr. Victor Spanioli, a DSI researcher, conducted an investigation at Site #31. DSI found the following two protocol violations:

- The eligibility criteria in Study III, excluded patients who were using concomitant medications known to prolong the QT interval. However, one patient who was enrolled in Study III received digoxin, a medication that is known to prolong the QT interval.
- Study III required recording of all AEs on the Case Report Form. However, one patient (the same patient who taking concomitant digoxin) experienced a post-dosing pre-colonoscopy hypoglycemic episode which was not reported as an AE.

Between September 28, and October 6, 2005, Mr. Robert Steyert, a DSI researcher, conducted an investigation at Site #12. DSI found the following protocol violation:

Study III required a complete physical examination at the Screening Visit. However, six patients did not have HEENT, Endocrine/Metabolic, Neurologic, Hematologic/Lymphatic, and Musculoskeletal examinations.

Between October 20 and November 1, 2005, Mr. Thomas Nojek, a DSI researcher, conducted an investigation at Site #3 in Study III. According to the DSI report, "From our review of the establishment inspection report and the documents submitted with that report, we conclude that, except for minor deficiencies, you adhered to the applicable statutory requirements and FDA

regulations governing the conduct of clinical investigations and the protection of human subjects" at Site #3 in Study III.

According to all of the DSI audits, the data from all three sites in Study III can be used in support the NDA. For more details about the DSI audits, please see Ni Aye Khin's reports about the three DSI audits.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all of the studies in the OsmoPrep NDA were conducted according to the applicable guidelines for good clinical practice and the applicable laws and regulations of the United States.

In all three studies, each patient was provided with oral and written information describing the nature and duration of the study. Written informed consent form was signed voluntarily by each patient prior to study entry in all the studies.

4.6 Financial Disclosures

According to the sponsor (InKine), all of the clinical investigators — involved in the submitted studies to NDA 21-892 — have not entered into any financial arrangement with InKine whereby the value of compensation could be affected by the outcome of the studies as defined in 21 CFR 54.2(a). Furthermore, according to the sponsor, all of the investigators did not disclose any proprietary interest in OsmoPrep or any significant equity interest in InKine as defined in 21 CFR 54.2(b). Finally, no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There is no human pharmacokinetic and bioavailability data in this NDA.

5.2 Pharmacodynamics

The sponsor conducted one pharmacodynamic (PD) study to satisfy the DGP's concern regarding a possible purgative effect of PEG 8000, a component of the OsmoPrep drug product. Please see Section 2.5 (Presubmission Regulatory Activity) for discussions between the DGP and the sponsor regarding this study. The PD study is presented below.

Title for Study INKP-102-04-02 (Study I): *"Purgative Effect and Safety of Polyethylene Glycol 8000 (PEG 8000, NF) compared to Inactive Vehicle: A Randomized, Double-Blinded, Single Center Trial in Healthy Male Volunteers."*

Study Objective: The primary objective of this study was to compare the purgative effect of PEG-

8000, NF in the inactive vehicle with that of inactive vehicle (Crystal Light®, a lemonade diet drink reconstituted in water) in healthy male volunteers.

The secondary objectives were to evaluate the safety and tolerability of PEG-8000, NF.

Study Design: This was a randomized, double-blind, single-center, 2-period crossover, pharmacodynamic, phase 1 study in the United States in healthy male subjects. Subjects were randomized to receive one of the following two dosing sequences: Sequence A (PEG 8000 and inactive vehicle in Period 1 **and then** inactive vehicle in Period 2) or Sequence B (inactive vehicle in Period 1 **and then** PEG 8000 and inactive vehicle in Period 2). Between the two sequences, subjects had a two-week washout period.

Eligibility Criteria: Table 4 displays the eligibility criteria of Study I.

Table 4: Eligibility criteria of Study I

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ Adult males, 18-45 years of age; ➢ Ability to communicate effectively with study personnel; ➢ Subjects were within 20% of the normal weight for their height; ➢ Subjects experienced bowel movements at least every other day without laxative use; ➢ Subjects provided written informed consent.	➢ Renal insufficiency (defined as serum creatinine >1.4 mg/dL); ➢ Known or suspected abnormalities in serum electrolytes or blood count; ➢ Gastrointestinal, heart or liver disease of any kind; ➢ Ascites or untreated dysrhythmias; ➢ Use of antibiotics within 6 months prior to the start of study; ➢ Receipt of any investigational product, or participation in a drug study, within 30 days prior to receiving test article (or within 60 days for investigational drugs with an elimination half-life greater than 15 days); ➢ Treatment with any purgative preparation within 14 days of the Screening Visit; ➢ Use of any complementary or alternative medicine; ➢ Known allergy or hypersensitivity to PEG; ➢ Use of alcohol within 3 days prior to either of the Visits 1 or 2; ➢ History or episode of acute gastroenteritis within the previous 60 days; ➢ History of laxative use (including fiber supplements) within the past 30 days; ➢ Known allergy or intolerance to any of the ingredients contained in Crystal Light, including aspartame (subjects with phenylketonuria were excluded); ➢ No bowel movement during the Baseline Period of Visit 1, more than 6 bowel movements during the Baseline Period, or any bowel movement rated "7" (watery) on the Bristol Stool Scale; ➢ Any other clinically significant disease or finding that, in the opinion of the investigator, would expose the subject to an increased risk of a significant AE event or would interfere with the assessments of efficacy and safety during the course of this study or previous enrollment in this study.

Reference: Final Study Report for Study I, Page 23

Drugs used in Study I: Subjects were randomized to receive one of the following two dosing sequences: Sequence A (PEG 8000 and inactive vehicle in Period 1 **and then** inactive vehicle in Period 2) or Sequence B (inactive vehicle in Period 1 **and then** PEG 8000 and inactive vehicle in Period 2). The inactive vehicle was Crystal Light, a lemonade diet drink.

In the PEG 8000 and the inactive vehicle phase, subjects took five doses of a solution of 670.4 mg of PEG 8000 dissolved in 240 mL of Crystal Light every 15 minutes over one hour, from 6 PM to 7 PM on Day 4. Additionally, these subjects took another 5 doses of this PEG 8000/Crystal Light solution over one hour from 6 AM to 7 AM on Day 5. Thus, the total PEG 8000 dose given to each subject during the Observational Period was 6.7 grams [the amount contained in 40 OsmoPrep tablets (the largest OsmoPrep dose in Studies II and III)] in 2.4 Liters of Crystal Light.

In the inactive vehicle phase, subjects took five doses of 240 mL of Crystal Light every 15 minutes over one hour, from 6 PM to 7 PM on Day 4 and another five doses of 240 mL of Crystal Light every 15 minutes over one hour, from 6 AM to 7 AM on Day 5. Thus, subjects received 2.4 Liters of Crystal Light.

Medical Reviewer's Comments: The amount of PEG 8000 used in Study 1 (6.7 grams) is equivalent to the amount used in 40 OsmoPrep tablets containing 60 grams of sodium phosphate. The amount of PEG 8000 in Study I is actually 25% greater than the amount of PEG 8000 in the sponsor's proposed 48 gram OsmoPrep dosing regimen.

Schedule of Procedures and Evaluations in Study I: The aim of the study was to replicate as closely as possible the study drug dosing prior to a colonoscopy in Studies II and III.

In Study I, subjects had a 48-hour Baseline Period (from 6 PM on Day 2 to 6 PM on Day 4) in which all their bowel movements (BMs) were collected, assessed for consistency, and weighed. The frequency of the patient's BMs was also recorded. Subsequent to the Baseline Period, subjects entered the 17-hour Observation Period (from 6 PM on Day 4 to 11 AM on Day 5). At the start of the Observation Period (from 6 PM to 7 PM), subjects took half of the study treatment and took the remaining half of the study treatment from 6 to 7 AM on Day 5..

Subjects were maintained on a standardized 2000-calorie, 22 grams of fiber per day diet on Days 1, 2, and 3). On Day 4 of each period, subjects had a low fiber breakfast followed by clear liquids for the rest of the day. On Day 5 of each period (after test article administration), subjects were instructed to have nothing by mouth (NPO) until the end of the Observation period (11 AM).

Efficacy Endpoints in Study I: The primary efficacy endpoint in Study I was the change in daily mean total wet stool weight between the Baseline Period and the Observation Periods (adjusted for the differing durations of these two periods) in the per protocol population.

Secondary efficacy endpoints in Study I included:

- The change in wet stool weight per BM (the total stool weight divided by the number of BMs) from the Observation Period compared to the Baseline Period. The stool weights were adjusted for the varying durations of the Baseline and Observation Periods;
- The change in the number of BMs/day (adjusted for the varying durations of the Baseline and Observation Periods) from the Observation Period compared to the Baseline Period; and
- The change in stool consistency from the Observation Period compared to the Baseline Period.

Medical Reviewer's Comments: This medical officer believes that the sponsor attempted to follow the DGP's recommendations regarding this PD study.

This medical officer believes that the design of Study 1 suffers from the following weaknesses: Study 1 had a small sample size (only 15 subjects were in the efficacy population) and the Baseline Period (48 hours) and Observation Period (17 hours) were too short to accurately determine stool weight. Since stool weight is very variable, longer Baseline and Observation Periods would have more accurately reflected the stool weight.

Statistical Analysis: According to the sponsor, non-inferiority would be informally demonstrated if the differences from baseline (from the Observation Period) in stool weight due to PEG 8000 treatment minus inactive vehicle treatment were no more than slightly positive. The upper 97.5% confidence bound for the between-period difference, PEG 8000 minus inactive vehicle, was to be estimated using a random effects regression model. For this study, no margin of non-inferiority was specified.

Medical Reviewer's Comments: This medical officer agrees with the sponsor's statistical analysis plan in this small study.

Disposition in Study I: In Study I, 16 male subjects received study treatment (the safety population) and 15 subjects completed the study (per protocol population for the efficacy analysis). The mean age (standard deviation) of the 15 subjects was 26.2 (6.3) years, with a range of 19 to 41 years old. All subjects were male, and 53%, 27% and 20% of the subjects were Black, Caucasian, and Hispanic, respectively. All demographic characteristics were comparable among the two sequence groups. The mean body mass index was 25.1.

Medical Reviewer's Comments: The sponsor included 15 healthy male subjects in Study 1. This represents about three times the amount suggested by Dr. Korvick in the DGP. Thus, the sponsor made a good faith effort to follow the DGP's recommendations regarding the number of subjects in this study.

Efficacy Results: The primary efficacy endpoint was the change in mean daily stool weight (the mean daily stool weight in the Observation Period minus the mean daily stool weight in the Baseline Period). The change in mean daily stool weight for PEG 8000/Inactive Vehicle and the Inactive Vehicle groups were 3.4 grams/day and - 60.8 grams/day, respectively (See Table 5).

Table 5: Mean (SD) stool weight in grams/day in the per protocol population in Study I

	Baseline Period	Observation Period	Change (Observation –Baseline)
PEG 8000 and Inactive Vehicle* (n=15)	88.2 (50)	91.7 (87)	3.4 (114)
Inactive Vehicle* (n=15)	106.1 (72)	45.3 (71)	-60.8 (123)

SD = Standard Deviation; *The Inactive Vehicle was 2.4 liters of Crystal Light
Reference: Study I Final Report, Table 5, Page 44

Table 6 displays the individual efficacy data for each of the 15 subjects in Study I.

Table 6: Individual efficacy data (daily stool weight and consistency) in the 15 subjects in Study I

Subject #	Treatment	Period	Daily Stool Weight during Period (grams/day)	Mean Bristol Score[1]	Possible laxative effect[2]
1	PEG 8000	Baseline	52	3	No
	Vehicle	Baseline	18	3	
5	PEG 8000	Baseline	84	4	Possible
	PEG 8000	Observation	251	4	
	Vehicle	Baseline	106	4	
7	PEG 8000	Baseline	111	3	No
	Vehicle	Baseline	91	2	
	Vehicle	Observation	94	2	
8	PEG 8000	Baseline	74	3	No
	PEG 8000	Observation	82	4	
	Vehicle	Baseline	100	4.5	
11	PEG 8000	Baseline	155	4	No
	Vehicle	Baseline	137	3.5	
14	PEG 8000	Baseline	77	3	Possible
	PEG 8000	Observation	130	3	
	Vehicle	Baseline	95	4	
15	PEG 8000	Baseline	198	4.3	No
	PEG 8000	Observation	125	3.5	
	Vehicle	Baseline	145	3.3	
19	PEG 8000	Baseline	143	5	No
	PEG 8000	Observation	64	3	
	Vehicle	Baseline	42	4	
	Vehicle	Observation	108	4	
20	PEG 8000	Baseline	76	3.5	No
	PEG 8000	Observation	2	1	

	Vehicle	Baseline	38	3	
	Vehicle	Observation	145	4	
2	Vehicle	Baseline	64	2	
	Vehicle	Observation	217	4	No
	PEG 8000	Baseline	56	4	
4	Vehicle	Baseline	39	2	
	Vehicle	Observation	114	3	
	PEG 8000	Baseline	90	3	No
	PEG 8000	Observation	94	4	
6	Vehicle	Baseline	144	4	
	PEG 8000	Baseline	51	4	Possible
	PEG 8000	Observation	196	3	
9	Vehicle	Baseline	68	2	
	PEG 8000	Baseline	7	2	Possible
	PEG-8000	Observation	209	3	
16	Vehicle	Baseline	255	3.5	
	PEG 8000	Baseline	30	3	No
	PEG 8000	Observation	184	3	
12	Vehicle	Baseline	250	5.3	
	PEG 8000	Baseline	117	5.5	No
	PEG 8000	Observation	38	3	

1 The Bristol Stool Scale is a 7 point scale of stool consistency including 1 (separate hard lumps like nuts), 2 (sausage shaped but lumpy), 3 (like a sausage but with cracks on surface), 4 (like a sausage or snake, smooth, and soft), 5 (soft blobs with clear-cut edges), 6 (fluffy pieces with ragged edges, a mushy stool), and 7 (watery, no solid pieces)

2 Medical officer's recommendations regarding possible laxative effect of PEG 8000 on each subject

Reference: Adapted from Study 1 Final Report, Table 16.2.6-2, Pages 302-308

Medical Reviewer's Comments: No subject in Study I who received PEG 8000 had a mean Bristol Stool Scale Score of 5 (soft blobs with clear-cut edges), 6 (fluffy pieces with ragged edges, a mushy stool), or 7 (watery, no solid pieces). Thus, patients averaged either normal consistency or harder consistency. If PEG 8000 was a laxative, then subjects would likely have stools with mean Bristol Stool Scale Scores of 5, 6, or 7.

This medical officer believes that 11 (73%) of the 15 subjects in Study I did not have a laxative effect from PEG 8000 administration and the following supports this medical officer's conclusions:

- **Of the 11 subjects, 4 subjects (Subject # 1, 7, 11, and 2) did not have any BMs during the Observation Period after PEG 8000 administration. Since these 4 subjects did not have any BMs, PEG 8000 did not act as a laxative in these subjects.**
- **Of the 11 subjects, 6 subjects (Subject # 8, 15, 19, 20, 4, and 16) had much lower daily stool weights during the Observation Period compared to the Baseline Period. If PEG 8000 acted as a laxative in these patients, then the daily stool weights should have been much greater in the Observation Period compared to the Baseline Period.**

- **One additional subject (Subject # 12) did have higher daily stool weight during the Observation Period compared to the Baseline Period after PEG 8000 administration. However, Subject # 12 had very variable daily stool outputs (his baseline daily stool weight ranged from 59 to 376 grams/day). Therefore, this medical officer believes that one cannot say that PEG-8000 had a significant laxative effect in this patient.**

This medical officer believes that 4 (27%) of the 15 subjects in Study I may have had a laxative effect from PEG 8000 administration. These 4 subjects (Subject # 5, 14, 6, and 9) had greater daily stool weight in the Observation Period compared to the Baseline Period after PEG 8000 administration. However, this medical officer believes that about 3 (20%) of the 15 subjects in Study I may have had a laxative effect from inactive vehicle administration. These 3 subjects (Subject #19, 20, and 2) had greater daily stool weight in the Observation Period compared to the Baseline Period after inactive vehicle administration.

Since this PD study (Study I) and the non-clinical study were negative, this medical officer concludes that PEG 8000 does not have a clinically meaningful laxative affect.

5.3 Exposure-Response Relationships

Please see Sections 6.1.2, 6.1.3, and 6.1.4 for detailed information about the phase 2, dose-ranging, OsmoPrep trial (Study II).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Methods

The two OsmoPrep trials (Studies II and III) submitted in this application were used in the efficacy evaluation.

6.2 General Discussion of Endpoints

Study III
Study III had a total of 17 pre-specified efficacy endpoints including 1 primary, 6 investigator-based secondary, and 10 patient-based secondary endpoints.

Primary Efficacy Endpoint: The primary endpoint was response rate to treatment. A patient was considered to be a responder if Overall Colon Cleansing was rated by the **colonoscopist** as excellent (1) or good (2) according to a 4-point Colonic Content Scale (see Table 7). A patient was considered a non-responder if their overall colon cleansing score was rated by the colonoscopist as fair (3) or inadequate (4). Colonic contents were defined as all liquid, semisolid, and solid material in the lumen of the colon, seen during colonoscopy.

Table 7: Four-point Colonic Content Scale

GRADE	#	DEFINITION
Excellent	1	>90% of mucosa seen, mostly liquid **colonic contents***, minimal suctioning needed for adequate visualization
Good	2	>90% of mucosa seen, mostly liquid **colonic contents***, significant suctioning needed for adequate visualization
Fair	3	>90% of mucosa seen, mixture of liquid and semisolid **colonic contents***, could be suctioned and/or washed
Inadequate	4	<90% of mucosa seen, mixture of semisolid and solid **colonic contents*** which could not be suctioned or washed

* Colonic contents were defined as all liquid, semisolid, and solid material in the lumen of the colon.
Reference: Section 9.5.4.1, Page 27

Medical Reviewer's Comments: The primary efficacy scale (Colonic Content Scale) is based on a Likert scale; however, the four possible responses are not discrete from one another. The definition of good (2) overlaps with the definition of fair (3). Both responses (1) and (2) are identical in the amount of visualized colon lumen seen (greater than 90%). Additionally, patients who have "mostly liquid colonic contents" also have a "mixture of liquid and semisolid colonic contents". Furthermore, patients who have colonic contents that needs "significant suctioning" also "could be suctioned and/or washed". Thus, the responses of good (2) and fair (3) can not be distinguished clinically. Since the responses of (2) and (3) in the primary efficacy assessment can not be distinguished clinically, the primary efficacy responder analysis is not adequate to determine the efficacy of the bowel preparations.

The sponsor's proposed responder definition is a lower standard, then primary efficacy assessments in other bowel preparation trials.

This medical officer recommends defining a responder as a patient who achieves a (1) on the four-point colonic content grading scale (the primary efficacy assessment). In this case, a non-responder is a patient who achieves a (2), (3), or (4) grade.

Alternatively, a responder could be defined as a patient who achieves a (1), (2), or a (3) on the four-point colonic content grading scale. In this case, a non-responder is a patient who achieves a (4) grade. In this responder definition, responders are patients who have > 90% of mucosa seen in their colons.

Colonoscopist-Based Secondary Efficacy Endpoints: Study III had the following 6 colonoscopist-based secondary efficacy endpoints:

1) Mean overall quality of colon cleansing (i.e., the mean overall colon cleansing score);
2) Ascending colon cleansing response rate;
3) Mean ascending colon cleansing score;
4) Percent of patients that will require colon re-examination within 3 months due to inadequate preparation (according to the colonoscopist);

5) Amount of irrigation used (no irrigation used, < 50 mL, 50-100 mL, or > 100 mL); and
6) Duration of procedure.

Patient-Based Secondary Efficacy Endpoints: Study III had the following 10 patient-based secondary efficacy endpoints:

1) Percentage of patients who took all of the study drug regimens;
2) Easiness or difficulty taking the study drug (easy, fairly easy, slightly difficult, or difficult);
3) Taste of the study drug (no taste, slight taste, bad taste but tolerable, or very bad taste and not tolerable;
4) Easiness or difficulty in drinking the prescribed liquids (easy, fairly easy, slightly difficult, or difficult);
5) Intensity of nausea (none, mild, moderate, or severe)*;
6) Intensity of vomiting (none, mild, moderate, or severe)*;
7) Intensity of bloating (none, mild, moderate, or severe)*;
8) Intensity of abdominal pain (none, mild, moderate, or severe)*;
9) Percentage of patients who would take the study preparation in the future, if they needed to have another colonoscopy; and
10) Percentage of patients who would be more likely to have a repeat colonoscopy if the study preparation they just received was available.

*The intensity of patient symptoms was graded on the following a four level scale:

- none (I did not experience this);
- mild (I did experience this, but it did not interfere with my activities);
- moderate (I did experience this, and it did interfere with my activities); or
- severe (I did experience this, and it prevented me from performing my activities).

Study II

Study NKP-102-03-01 (Study II) had 2 co-primary efficacy endpoints, 6 colonoscopist-based secondary efficacy endpoints, and 1 patient-based secondary efficacy endpoint.

Co-Primary Efficacy Endpoints: The co-primary efficacy endpoints in Study II were the following:

1) Overall quality of colon cleansing: A patient was considered to be a responder if Overall Colon Cleansing was rated by the colonoscopist as excellent (1) or good (2) according to a 4-point Colonic **Content** Scale (see Table 7). Colonic contents were defined as all liquid, semisolid, and solid material in the lumen of the colon, seen during colonoscopy. This endpoint was identical to the primary efficacy endpoint in Study III.
2) Overall quality of colon cleansing: A patient was considered to be a responder if Overall Colon Cleansing was rated by the colonoscopist as excellent (1) or good (2) according to a 4-point Colonic **Stool** Scale (see Table 8). In the Colonic Stool Scale, colonoscopists judged the quality of the preparation based on only stool; whereas, in the colonic content grading scale colonoscopists judged the quality of the preparation based on all colon contents including stool and other material in the lumen of the colon.

Table 8: Four-point Colonic Stool Scale

GRADE	#	DEFINITION
Excellent	1	>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization
Good	2	>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	3	>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	4	<90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

Reference: Study II, Appendix 3, Page 338

Colonoscopist-Based Secondary Efficacy Endpoints: The 6 colonoscopist-based secondary efficacy endpoints in Study II were the following:

1) Mean overall colon content cleansing score;
2) Mean overall colonic stool grading score;
3) Ascending colon content cleansing response rate;
4) AC colonic stool cleansing response rate;
5) Percent of patients that had inadequate preparation; and
6) Duration of procedure.

Patient-Based Secondary Efficacy Endpoints: The 1 patient-based secondary efficacy endpoint in Study II was the following: patient compliance with dosing.

Medical Reviewer's Comments: This medical officer reviewed the primary efficacy assessments for the all of the submitted phase 3 clinical trials for the following approved bowel preparations: GoLYTELY (NDA 19-011), Colyte (NDA 18-983), OCL Solution (NDA 19-284), NuLYTELY (NDA 19-797), Visicol (NDA 21-097), and HalfLytely (NDA 21-551). Additionally, this medical officer reviewed the primary efficacy scales and assessments for MOVIPREP (NDA 21-881), an investigational PEG-based bowel preparation under NDA review. Please see Table 9 for more details.

The primary efficacy scale in OsmoPrep Study III used a very similar to the primary efficacy scale used in the two Visicol phase III trials (submitted in NDA 21-097). The only difference between the scales was that Visicol used the term "stool" and the one phase III OsmoPrep study used the terms "colonic contents" in the primary efficacy scale. This medical officer believes that OsmoPrep scale is an improvement compared to the Visicol scale because it includes all colonic contents including stool and non-stool content.

One of the two co-primary efficacy endpoints (stool) in OsmoPrep Study II used the identical efficacy scale as used in the Visicol studies and the second co-primary efficacy endpoint (colon content) used the identical efficacy scale as used in OsmoPrep Study III. OsmoPrep Studies II

and III used a responder definition for the primary efficacy assessments; whereas, the Visicol phase 3 studies used the mean of the four-point scale for the primary efficacy assessment.

The NuLYTELY and HalfLytely phase 3 studies had identical primary efficacy scales. However, the NuLYTELY studies used a rigid analysis and the HalfLytely studies used a responder definition for the primary efficacy assessment.

The procedures in the bowel preparation trials were different. The bowel preparation trials differed in the length of time between the last dose of bowel preparation and colonoscopy, the timing of the last meal allowed, and the diet allowed in the last meal before colonoscopy. The differences in study conduct and the differences in primary efficacy scales, assessments, and statistical analysis makes it very difficult to compare the efficacy among these bowel preparation trials.

Table 9: Primary efficacy scales and assessments for the important phase 3 prescription colon preparation studies submitted in colon preparation NDAs

Drug	NDA	Comparators	Primary Efficacy Scale	Primary Efficacy Assessment
GoLYTELY	19-011	1) GoLYTELY 2) Magnesium citrate, bisacodyl, and enema	**Adequate:** Sufficient visualization to satisfy the clinical indication for the procedure; or **Not adequate:**	Responders were adequate
NuLYTELY	19-797	1) NuLYTELY 2) GoLYTELY	**Excellent (4):** No more than small bits of adherent feces/fluid; **Good (3):** Small amounts of feces or fluid not interfering with exam; **Fair (2):** Enough feces or fluid to prevent a completely reliable exam; **Poor (1):** Large amounts of fecal residue, additional cleansing required.	Rigid analysis (takes into account all four numbers of the scale)
Visicol	21-097	1) Visicol 2) NuLYTELY	**Excellent (1):** >90% of mucosa seen, mostly liquid **stool**, minimal suctioning needed for adequate visualization; **Good (2):** >90% of mucosa seen, mostly liquid **stool**, significant suctioning needed for adequate visualization; **Fair (3):** >90% of mucosa seen, mixture of liquid and semisolid **stool**, could be suctioned and/or washed; **Inadequate (4):** <90% of mucosa seen, mixture of semisolid and solid **stool** which could not be suctioned or washed.	Mean score

HalfLytely	**21-551**	**1) HalfLytely** **2) NuLYTELY**	**Excellent (4):** No more than small bits of adherent feces/fluid; **Good (3):** Small amounts of feces or fluid not interfering with exam; **Fair (2):** Enough feces or fluid to prevent a completely reliable exam; **Poor (1):** Large amounts of fecal residue, additional cleansing required.	**Responders are Excellent or Good**
MOVIPREP*	**21-881**	**German Study** **1) MOVIPREP** **2) GoLYTELY** **French Study** **1) MOVIPREP** **2) Oral Sodium Phosphate Solution**	**Very Good (4):** Colon empty and clean; **Good (3):** Presence of clear liquid in the gut, but easily to be removed by suction; **Moderate (2):** Brown liquid/semisolid remaining amounts of stool, fully removable by suction; **Bad (1):** Semisolid amounts of stool, partially removable, risk of incomplete gut mucosa visualization; **Very Bad (0):** Semisolid/solid stool; colonoscopy incomplete or required termination	**Responders are Very Good, Good, or Moderate in all five colonic segments**
OsmoPrep*	**21-892**	**1) OsmoPrep** **2) Visicol**	**Excellent (1):** >90% of mucosa seen, mostly liquid **colonic contents**, minimal suctioning needed for adequate visualization **Good (2):** >90% of mucosa seen, mostly liquid **colonic contents**, significant suctioning needed for adequate visualization **Fair (3):** >90% of mucosa seen, mixture of liquid and semisolid **colonic contents**, could be suctioned and/or washed **Inadequate (4):** <90% of mucosa seen, mixture of semisolid and solid **colonic contents** which could not be suctioned or washed	**Responders are Excellent or Good**

* Not approved. MOVIPREP is an investigational PEG-based drug product under NDA review.
All of the trials used non-inferiority statistical analyses
Reference: Data on file with the FDA

6.3 Study Design

Title for Study INKP-102-04-01 (Study III): ***"Colon Cleansing Efficacy and Safety of a New Microcrystalline Cellulose-Free Formulation of Sodium Phosphate Tablets (INKP-102) Compared to Visicol® Tablets (INKP-101): An Investigator-blinded, Randomized, Multicenter Trial."***

Study Objective: The primary objective of the study was to evaluate, by direct visualization, the colon cleansing efficacy of two dosing regimens of a new formulation of sodium phosphate tablets (OsmoPrep) compared to Visicol tablets in patients undergoing colonoscopy. The secondary objectives of the study were to determine whether the use of OsmoPrep compared to Visicol Tablets:

- Have comparable colon cleansing in the ascending colon;
- Have a similar patient acceptance profile;
- Have a similar, if any, impact on selected serum electrolytes (sodium, potassium, chloride, bicarbonate, phosphate, magnesium, and calcium); and
- Provide an acceptable safety profile.

Study Design: This was a randomized, single-blind (investigator), active-controlled, multicenter (32 sites), phase 3 trial of OsmoPrep for colonic preparation in patients scheduled to have an elective colonoscopy in the United States. Patients were randomized 1:1:1 to receive 40 tablets of Visicol (60 grams of sodium phosphate); 40 tablets of OsmoPrep (60 grams of sodium phosphate); or 32 tablets of OsmoPrep (48 grams of sodium phosphate) by mouth prior to the elective colonoscopy.

Medical Reviewer's Comments: This study was well-controlled and well designed. This study had an active control (the approved Visicol dosing regimen) and had a dose ranging control (two different amounts of OsmoPrep).

This study's blinding (investigator-blinded and open-label to the patient) is consistent with historical bowel preparation studies. Patient-blinding is difficult to perform in bowel preparation studies because the treatment regimens are vastly different (for example, treatments have different schedules and the amount and frequency of required concomitant clear liquids vary).

The duration of this controlled study is acceptable for the efficacy evaluation of bowel preparations in colonoscopy cleansing. The duration of this study is consistent with historical bowel preparation studies.

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Eligibility Criteria: Table 10 displays the eligibility criteria of Study III.

Table 10: Eligibility criteria of Study III

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ Male or nonpregnant, nonlactating females at least 18 years of age scheduled for colonoscopy; ➢ Females of childbearing potential were required to use an acceptable form of birth control and were required to have a negative serum (human chorionic gonadotropin; hCG) pregnancy test at screening. ➢ Women who were postmenopausal for ≥ 1 year or who had undergone a hysterectomy were not subject to pregnancy testing; ➢ Ability to swallow tablets the size of a multivitamin without difficulty; ➢ Able to communicate effectively with study personnel; and ➢ Provided written informed consent.	➢ Renal insufficiency (defined as serum creatinine > 2.0 mg/dL); ➢ Abnormal values of the following electrolytes in the serum at the time of screening: sodium, potassium, phosphorous, calcium, or magnesium; ➢ Uncontrolled congestive heart failure (American Heart Association Class III or IV); ➢ Ascites of any etiology; ➢ Untreated cardiac dysrhythmia; ➢ Current use of digitalis preparations or medications known to prolong QT interval; ➢ Myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft surgery within the previous 3 months; ➢ Unstable angina pectoris; ➢ Current acute exacerbation of chronic inflammatory bowel disease; ➢ Severe chronic constipation, defined as fewer than one bowel movement per week for a period >1 year; ➢ Ileus and/or acute obstruction; ➢ Ileostomy, right or transverse colostomy, subtotal colectomy with ileosigmoidostomy, with ≥ 50% of colon removed; only those patients with right or left hemicolectomy were eligible; ➢ Hypomotility syndrome, megacolon or idiopathic pseudo-obstruction; ➢ History of gastric stapling or bypass procedure; ➢ Known allergy or hypersensitivity to sodium phosphate salts, any other constituent of OsmoPrep (e.g., polyethylene glycol or magnesium stearate), Visicol Tablets, or any other constituent of Visicol (e.g., cellulose, silicon dioxide); ➢ Receipt of an investigational drug or product, or participation in a drug study within 30 days prior to receiving study medication (or within 60 days for investigational drugs with an elimination half-life greater than 15 days); ➢ Previous enrollment in this study; ➢ Treatment with any other sodium phosphate preparation within 14 days prior to colonoscopy; ➢ Any other clinically significant disease or finding that, in the opinion of the investigator, would have exposed the patient to an increased risk of a significant AE or would have interfered with the assessments of efficacy and safety during the course of this study.

Reference: Study III Report, Sections 9.3.1 and 9.3.2, Pages 17-18

Medical Reviewer's Comments: This medical officer agrees with the exclusion of any disorder that may be exacerbated by electrolyte abnormalities including congestive heart failure, ascites, cardiac ischemia, renal failure, and untreated arrhythmias.

The protocol should have also excluded patients with a history of seizures because according to the PRECAUTIONS section of the Visicol label, "there have been reports of generalized tonic-clonic seizures and/or loss of consciousness associated with Visicol use in patients with no prior history of seizures. Cases of seizure were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypochloremia, hypocalcemia, hypomagnesemia), and low serum osmolality. Neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities."

This medical officer agrees that all patients should have normal electrolyte levels prior to receiving sodium phosphate colonic preparations. Visicol was associated with electrolyte abnormalities including about 95% hyperphosphatemia, 20% hypokalemia in the two phase III trials.

Additionally, this medical officer believes that patients taking concomitant medications that are known to prolong the QT interval should have been excluded from this study.

Drugs used in Study III: Patients were randomized 1:1:1 to one of the following three groups: 40 tablets of Visicol (60 grams of sodium phosphate); 40 tablets of OsmoPrep (60 grams of sodium phosphate); or 32 tablets of OsmoPrep (48 grams of sodium phosphate). Please see Table 11 for the dosing regimens of the three treatment groups in Study III.

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Table 11: Dosing Regimens in Study III

Treatment Groups	Dosing Regimens	Total # of tablets*	Total amount of clear liquid
60 grams of OsmoPrep	The night before colonoscopy: Starting at 6:00 PM, patients were to take 4 tablets at a time with 240 mL of clear liquid every 15 minutes (over 1 hour) The day of the colonoscopy: Starting 3 to 5 hours prior to the colonoscopy, patients were to take 4 tablets at a time with 240 mL of clear liquid every 15 minutes (over 1 hour)	40 (20 in PM and 20 in AM)	2.4 liters
48 grams of OsmoPrep	The night before colonoscopy: Starting at 6:00 PM, patients were to take 4 tablets at a time with 240 mL of clear liquid every 15 minutes (over 1 hour) The day of the colonoscopy: Starting 3 to 5 hours prior to the colonoscopy, patients were to take 4 tablets at a time with 240 mL of clear liquid every 15 minutes (over 0.5 hours)	32 (20 in PM and 12 in AM)	1.92 liters
60 grams of Visicol	The night before colonoscopy: Starting at 6:00 PM, patients were to take 3 tablets at a time with at least 240 mL of clear liquid every 15 minutes (over 1.5 hours) The day of the colonoscopy: Starting 3 to 5 hours prior to the colonoscopy, patients were to take 3 tablets at a time with at least 240 mL of clear liquid every 15 minutes (over 1.5 hours)	40 (20 in PM and 20 in AM)	At least 3.36 liters

* Each tablet contains 1.5 grams of sodium phosphate
Reference: Study III protocol.

Medical Reviewer's Comments: The three study regimens differed in the length of time between the last dose and the start of the colonoscopy. This time duration was 1.5 to 3.5 hours, 2 to 4 hours, and 2.5 to 4.5 hours in the 60 gram Visicol, 60 gram OsmoPrep, and 48 gram OsmoPrep regimens, respectively. The amount of time between the last dose of bowel preparation and colonoscopy may influence the efficacy of the treatment groups.

Selection of the dose in Study III: The doses selected in this phase 3 study were chosen based on previous clinical studies, Study II (the dose-ranging phase 2 study), and from doses established by the approval of Visicol as a colon-cleansing agent.

Selection of the dosage regimen in Study III: According to the sponsor, both OsmoPrep dose regimens were selected for use in Study III based on their efficacy and safety profiles in Study II. The two OsmoPrep dosage regimens selected for Study III, were among the most efficacious dosage regimens in Study II. The split dosage regimens demonstrated numerically-improved efficacy compared to the evening-only doses in Study II. Visicol (60 grams) was selected as an active control

in order to compare the OsmoPrep doses to an established, FDA-approved colonic preparation product.

Schedule of Procedures and Evaluations in Study III: See Table 12 for a schedule of the procedures and evaluations in Study III.

Table 12: Procedures and evaluations in Study III

	Screening Visit 0[a]	Visit 1[b]	Telephone Follow-up[c]
Informed consent	X		
History and physical	X	X	
Weight and height	X	X[d]	
Vital signs	X	X	
Postural hypotension test	X	X	
Laboratory evaluations	X	X	
Dispense study medication	X		
Collect and record remaining study medication		X	
Record any adverse events		X	X[e]
Complete concomitant medications page of CRF	X	X	
Administer Patient Questionnaire		X	
Colonoscopy		X	
Complete Physician Questionnaire		X	
Telephone contact for AE follow-up			X
Complete "End of Study" page of CRF			X

a: Up to 14 days prior to colonoscopy
b: Day of scheduled colonoscopy
c: Two weeks (± 3 days) after colonoscopy (or after last intake of study medication for patients who took study medication but did not have a colonoscopy)
d: Weight only
e: Only AEs that required hospitalization, an emergency room visit, or which precipitated a visit to a health care provider were recorded as AEs during this visit.
Reference: Study III, Section 9.5.3, Table 9.5-1, Page 26

Screening Phase (Visit 0): After informed consent had been obtained, screening evaluations were to be performed within the 14 ± 3 days prior to the colonoscopy to verify that the patient satisfied all of the eligibility criteria.

These evaluations included a complete medical history, physical examination (including height and weight), and vital signs monitoring (heart rate, blood pressure, temperature, respiration rate and evaluation of postural hypotension). For women of childbearing potential (including women with a

prior tubal ligation who were still menstruating), a serum pregnancy test was performed (serum HCG). Screening lab tests included: serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphate and magnesium), BUN, and creatinine.

Patients were randomized and given study medication at the screening visit and they were instructed not to begin the study medication until they were notified by the study personnel. If patients had abnormal lab tests, then they were instructed not to take the study medication and they were to return the study medication. If patients qualified for the study (including no abnormal labs) then they were instructed by telephone to begin the study medication, the evening prior to the colonoscopy. Patients — who were randomized to a study treatment and then later determined to be ineligible on the basis of laboratory tests — were not included in the safety or efficacy analyses.

At the screening visit, dietary requirements were issued to the patient: On the day before colonoscopy, patients were permitted to eat a light breakfast before 12:00 noon (e.g., pulp-free beverages, and low-fiber, low-fat foods). With the exception of a light breakfast, patients were instructed not to eat solid food and to drink only clear liquids.

Patients were evaluated at the screening visit for the presence of symptomatic postural hypotension, defined as (1) orthostatic changes in vital signs with (2) postural symptoms during the test of postural hypotension. The postural hypotension test was conducted as follows: the examiner assessed and recorded the patient's blood pressure (BP) and pulse after the patient had been supine for at least 3 minutes. Thereafter, the patient stood up, and the examiner monitored the patient for the development of light-headedness, dizziness, or syncope. After the patient had been standing for 3 minutes, the BP and pulse measurements were repeated. Orthostatic changes in vital signs were defined as:

- An orthostatic pulse increase of 30 beets per minute (bpm) or greater, accompanied by symptoms;
- An orthostatic decrease in systolic BP of 25 mmHg or greater, accompanied by symptoms; or
- An orthostatic decrease in diastolic BP of 10 mmHg or greater, accompanied by symptoms.

Postural symptoms (during the test of postural hypotension) included the following:

- Lightheadedness lasting for at least 30 seconds;
- Dizziness lasting for at least 30 seconds; or
- Syncope of any duration.

Medical Reviewer's Comments: **The timing of the last meal can influence the efficacy of the treatment groups. Patients who eat solid food closer to the colonoscopy are more likely to have poorer colon cleansing. Since this study established uniform rules for all the treatment groups, the timing of the last solid meal was acceptable.**

Since this study's dietary procedures were different than other bowel preparation studies, it may be difficult to compare these results to other bowel preparation studies.

should be placed in the CLINICAL STUDIES section of the proposed OsmoPrep label.

The laboratory tests did not include a complete blood count (CBC), liver enzyme tests (such as alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, and alkaline phosphatase), or coagulation tests (such as INR and PTT).

No screening ECGs were performed on any of the study patients. According to the WARNINGS section of the approved Visicol label, "Administration of other sodium phosphate products ... has resulted in fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias". In addition, Visicol has been associated with QT prolongation in Visicol clinical trials. Thus, clinical trials of sodium phosphate products (such as Visicol and OsmoPrep) should have baseline ECGs, so patients with prolonged QT and arrhythmias can be excluded.

All patients in the study were instructed not to take the study drug until their baseline laboratory tests were completed and were within normal limits. This study conduct was acceptable because "severe electrolyte abnormalities" have been associated with sodium phosphate preparations including Visicol.

The Day Prior to Colonoscopy: The patients began self-administration of study medication at 6 PM, the evening prior to their colonoscopy after they received confirmation of eligibility from the study site.

Colonoscopy Day: The patients self-administered study medication beginning 3 to 5 hours prior to their scheduled colonoscopy.

Immediately before colonoscopy was performed (but before the patient was sedated), the patient received a physical examination (including body weight and vital signs with a test for postural hypotension). Any AEs that were noted since the patient's first dosing of study medication were recorded, as was concomitant medication usage. Laboratory samples were obtained for serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphate and magnesium), BUN, and creatinine.

Patients orthostatics were repeated on the colonoscopy day (see the screening visit for details).

Patients were administered the "Patient Questionnaire" with the following questions:

1) Did you take all of your sodium phosphate tablets?
2) If no, how many did you take in the morning and in the evening?
3) How easy or difficult was it for you to take the study preparation (easy, fairly easy, slightly difficult, or difficult)?
4) How did the study preparation taste (no taste, slight taste, bad taste but tolerable, or very bad taste and not tolerable)?

5) How easy or difficult was it for you to drink the amount of liquids prescribed liquids (easy, fairly easy, slightly difficult, or difficult)?
6) Did you experience any of the following side effects (nausea, vomiting, bloating, or abdominal pain)?
7) For each of the above side effects, did you have mild (I did experience this, but it did not interfere with my activities), moderate (I did experience this, and it did interfere with my activities), or severe (I did experience this, and it prevented me from performing my activities) symptoms?
8) In the future, if you need to have another colonoscopy, would you take the study preparation you just received?
9) Choose one of the following statements:

   - At no time during the entire study did I say or do anything to let my study physician know what study medication I took, or the response I had to the study medication; or
   - During the study, I discussed with my study physician what study medication I took and/or the response I had to the study medication.

The responses to these questions formed several of the patient-based secondary efficacy endpoints.

During and/or following the colonoscopy, the following procedures were performed:

1) Colonoscopy and investigator evaluation of the effectiveness of the bowel-cleansing regimen (documented on the Physician Questionnaire).
2) Videotape recording of the colonoscopy (at 2 specified sites out of 32 total sites).
3) Study coordinator review of the Physician Questionnaire for completeness.
4) Study medication accountability and compliance was performed.

Medical Reviewer's Comments: **CBCs, liver tests, and coagulation blood tests were not performed during Visit 1 or at any other time during the treatment period.**

ECGs were not performed during Visit 1 (on the day of colonoscopy), at screening, post colonoscopy, or at any other time during the treatment period. This medical officer believes that ECGs should have been performed throughout this study because sodium phosphate products have been associated with arrhythmias and QTc prolongation.

Concomitant Therapy during the Treatment Period: Any medications required by eligible patients for the management of concomitant medical conditions were allowed. Chronic narcotic use and the use of drugs that could have affected the gastrointestinal motility (such as laxatives, stool softeners, promotility agents, antidiarrheal medications, purgatives, and enemas) were prohibited. Patients were to have discontinued such medication use prior to dosing with the study medication. All non-systemically absorbed medications (e.g., milk of magnesia, MiraLax) were to have been held for 24 hours prior to dosing with study medication. Systemically absorbed medications were to be held for at least 24 hours prior to dosing with study medication. The half-life and length of activity of systemically absorbed medications influenced the time they were held prior to dosing.

Post Colonoscopy Follow-Up: All patients were to have one follow-up telephone call 11 to 17 days after colonoscopy. Investigators asked patients about AEs they experienced since the colonoscopy. Health problems that required a healthcare provider visit (including a hospitalization or an emergency room visit) were captured as adverse events, which were followed-up until resolved or fully characterized. Additionally, if patients developed an AE earlier during the treatment period that had not resolved, follow-up information was collected during this telephone call. In contrast, if patients did not seek medical attention for certain medical problems that occurred after their colonoscopy, then these events were not captured as AEs.

Medical Reviewer's Comments: This medical officer believes that patients should have had one post colonoscopy safety visit including complete histories, physical exams, laboratory testing, and ECGs.

Sodium phosphate products such as Visicol have been associated with the development of renal failure (including phosphate nephropathy). Several of these patients who developed phosphate nephropathy (associated with sodium phosphate bowel preparations) were diagnosed several weeks after their colonoscopy. Thus, a follow-up safety visit should be performed in all sodium phosphate bowel preparation trials.

Statistical Methods for the Primary Efficacy Endpoint in Study III: The protocol-specified primary endpoint analysis involved a test of non-inferiority, which was conducted in the following sequential manner:

1) The response rate for the 60 gram OsmoPrep treatment group was first compared to the Visicol control treatment group; if the lower limit of the 97.5% one-sided confidence interval of the difference in response rates (OsmoPrep minus Visicol) was $\geq$ -10%, and the resulting p-value for non-inferiority test was no more than 0.05, then the 60 gram OsmoPrep treatment group was considered non-inferior to the Visicol treatment group.
2) If, and only if, the non-inferiority of the 60 gram OsmoPrep treatment group was previously established, the 48 gram OsmoPrep treatment group was then compared to the Visicol treatment group (using a non-inferiority analysis with the same parameters described above).

Medical Reviewer's Comments: The statistical analysis plan including the non-inferiority margin was acceptable.

Statistical Populations in Study III: The following three populations were pre-specified in Study III:

1) All assessed patients (AAP) population: Patients who ingested at least one sodium phophate tablet and had a colonoscopy. The primary and secondary efficacy endpoints were performed on this AAP population.
2) Per protocol (PP) population: Patients who took at least 90% of their tablets within 2 hours (± 2 hours) of the recommended dosing time and had a colonoscopy.
3) Safety population: Patients who ingested at least one sodium phosphate tablet.

Title for Study NKP-102-03-01 (Study II): ***"A Randomized, Investigator-Blinded Comparison of Visicol® Tablets to a New Microcrystalline Cellulose-Free Formulation of Sodium Phosphate Tablets for Colon Cleansing"***

Study Objective: The primary objective of the study was to evaluate, by direct visualization, the colon cleansing efficacy of 6 dosing regimens of a new formulation of sodium phosphate tablets (OsmoPrep), compared to marketed Visicol® Tablets in patients undergoing colonoscopy. The secondary objective of the study was to evaluate the safety of various dosing regimens of OsmoPrep tablets.

Study Design: This was a randomized, multicenter (6 sites), single-blinded (investigator), phase 2 study of OsmoPrep in patients scheduled to have an elective colonoscopy in the United States. Patients were randomized to one of seven sodium phosphate regimens including six OsmoPrep regimens (Arms B, C, D, E, F, and G) and one Visicol regimen (Arm A). The Visicol regimen, the approved and marketed dosage regimen, contains 60 grams of sodium phosphate split between the day before the colonoscopy and the morning of the colonoscopy. See Table 13 for the seven treatment groups in Study II.

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Table 13: The seven treatment groups in Study II

Treatment Arm	Dosing Instructions
A	Visicol® Tablets (INKP-101) (60 g sodium phosphate) by mouth as follows: 20 tablets over 1.5 hours beginning at 6 PM the evening before colonoscopy and 20 tablets over 1.5 hours beginning 3 to 5 hours before colonoscopy, with tablets taken 3 at a time every 15 minutes with at least 8 oz of clear liquid (water, clear carbonated beverage or juice).
B	40 INKP-102 tablets (60 g sodium phosphate) by mouth as follows: 20 tablets over 1.5 hours beginning at 6 PM the evening before colonoscopy and 20 tablets over 1.5 hours beginning 3 to 5 hours before colonoscopy, with tablets taken 3 at a time every 15 minutes with at least 8 oz of clear liquid (water, clear carbonated beverage or juice).
C	40 INKP-102 tablets (60 g sodium phosphate) by mouth as follows: 20 tablets over 1 hour beginning at 6 PM the evening before colonoscopy and 20 tablets over 1 hour beginning 3 to 5 hours before colonoscopy, with tablets taken 4 at a time every 15 minutes with 8 oz of clear liquid (water, clear carbonated beverage or juice).
D	32 INKP-102 tablets (48 g sodium phosphate) by mouth as follows: 20 tablets over 1 hour beginning at 6 PM the evening before colonoscopy and 12 tablets over a half-hour period beginning at 10 PM the same evening, with tablets taken 4 at a time every 15 minutes with 8 oz of clear liquid (water, clear carbonated beverage or juice).
E	32 INKP-102 tablets (48 g sodium phosphate) by mouth as follows: 20 tablets over 1 hour beginning at 6 PM the evening before colonoscopy and 12 tablets over a half-hour period the next day beginning 3 to 5 hours before colonoscopy, with tablets taken 4 at a time every 15 minutes with 8 oz of clear liquid (water, clear carbonated beverage or juice).
F	28 INKP-102 tablets (42 g sodium phosphate) by mouth as follows: 20 tablets taken over 1 hour the evening before colonoscopy beginning at 6 PM and 8 tablets taken over 15 minutes starting at 9 PM the same evening, with tablets taken 4 at a time every 15 minutes with 8 oz of clear liquid (water, clear carbonated beverage or juice).
G	28 INKP-102 tablets (42 g sodium phosphate) by mouth as follows: 20 tablets beginning at 6 PM the evening before colonoscopy and 8 tablets the next day beginning 3 to 5 hours before colonoscopy, with tablets taken 4 at a time every 15 minutes with 8 oz of clear liquid (water, clear carbonated beverage or juice).

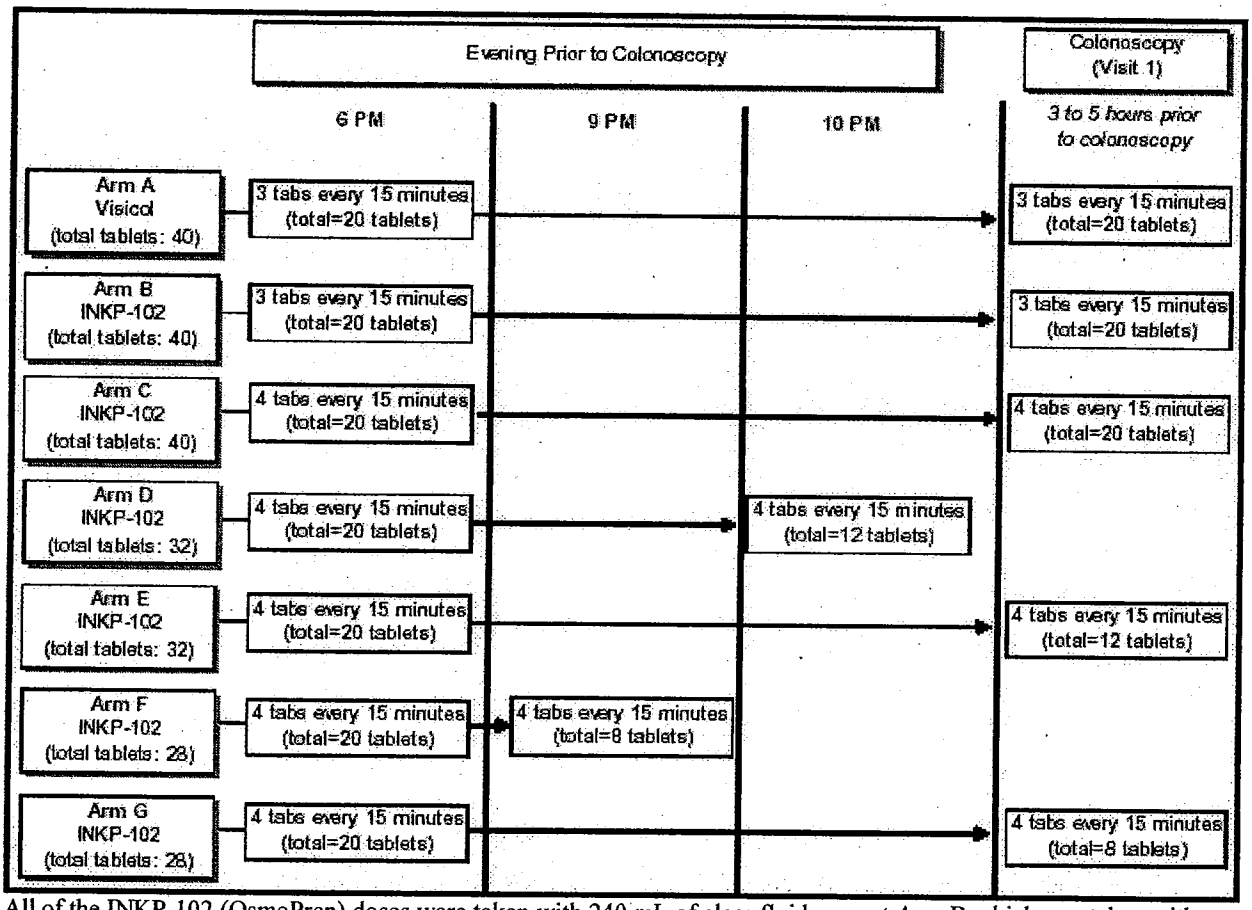
INKP-102 is a synonym for OsmoPrep
Reference: Study II Final Report, Section 9.4.1, Page 16

The six OsmoPrep dosage regimens differed in the following ways (see Table 14):

1) OsmoPrep regimens B and C contained 60 grams of sodium phosphate; OsmoPrep regimens D and E contained 48 grams of sodium phosphate, and OsmoPrep regimens F and G contained 42 grams of sodium phospate;
2) Of the six OsmoPrep regimens, four (B, C, E, and G) were split between the day before the colonoscopy and the day of the colonoscopy and two (D and F) were administered only during the evening prior to the colonoscopy.
3) The length of time that patients were required to finish the bowel preparation differed.
4) The amount of required clear liquid fluid differed between the regimens. OsmoPrep regimen B required at least 3.36 liters; OsmoPrep regimen C required 2.4 liters; OsmoPrep

regimens D and E required 1.92 liters; and OsmoPrep regimens F and G required 1.68 liters of clear fluid.

Table 14: The seven treatment groups in Study II



All of the INKP-102 (OsmoPrep) doses were taken with 240 mL of clear fluid, except Arm B which was taken with at least 240 mL of clear fluid. The one Visicol dose was taken with at least 240 mL of clear fluid.
Reference: Study II Final Report, Section 9.1, Figure 9.1-1, Page 12

Eligibility Criteria: The eligibility criteria in Study II were similar to the eligibility criteria in Study III (see Table 10).

Drugs used in Study II: Patients were randomized to one of seven treatment groups (six OsmoPrep groups and one Visicol group) in Study II. Visicol, the active control group, was dosed at the approved dose for colonoscopy preparation. All Visicol and OsmoPrep tablets contained 1.5 grams of sodium phosphate. See Tables 13 and 14 for the seven dosage regimens in Study II.

Selection of the dose in Study II: The doses selected in this dose-finding study were chosen based on previous Visicol clinical studies.

Selection of the dosage regimen in Study II: Various OsmoPrep dose regimens were chosen for this phase 2 study. Some of the dosage regimens reduced the time required to take the OsmoPrep tablets and reduced the amount of ingested clear fluid. According to the sponsor, if a bowel preparation can be administered in a shorter period of time and with less required fluid, then compliance may be increased. Increased compliance may improve efficacy.

Two of the OsmoPrep dosing regimens were evening-only and were intended to satisfy the wishes of endoscopists who did not want patients to get up early before a procedure to complete the dosing regimen, or anesthesiologists who required that the patient receive nothing by mouth (NPO) on the morning of the procedure.

Schedule of Procedures and Evaluations in Study II: See Table 15 for a schedule of the procedures and evaluations in Study II. On the day before the colonoscopy, patients were allowed to eat a light breakfast in the morning. After breakfast, patients were allowed to drink clear liquids (such as water, ginger-ale, apple juice, weak tea, or other colorless liquids) and they were instructed not to eat solid food.

Table 15: Schedule of procedures and evaluations in Study II

	Screening Visit 0[a]	Visit 1[b]
Informed consent	X	
History and physical	X	X
Weight and height	X	X[c]
Vital signs	X	X
Laboratory evaluations	X	X
Dispense study medication	X	
Collect and record remaining study medication		X
Record any adverse events		X[d]
Complete concomitant medications page of CRF	X	X
Administer Patient Questionnaire		X
Colonoscopy		X
Complete Physician Questionnaire		X
Complete "End of Study" page of CRF		X

a Up to 14 days prior to colonoscopy
b Day of scheduled colonoscopy
c Weight only
d AEs continuing at the end of the study were to be followed for 72 hours.
Reference: Study II Final Report, Section 9.5.2, Table 9.5-1, Page 20.

Medical Reviewer's Comments: The schedule of evaluations and procedures in Studies II and III were very similar (please see the schedule of evaluations and procedures for Study III in Table 12). Both studies had identical Patient Questionnaires, identical procedures for eating solid food and clear liquids, identical lab tests, identical orthostatic measurements, and other similar evaluations and procedures. Both Studies II and III had suboptimal follow safety evaluations (both did not have follow-up (post-colonoscopy) safety physical exams, laboratory testing, or ECG testing. Additionally, both Studies II and III had no baseline ECG testing.

Studies II and III had the following different evaluations and procedures:

- **Study II had less post-colonoscopy safety monitoring than Study III. Study III had a follow-up telephone call (14 days after the colonoscopy); whereas, Study II had no follow-up telephone call post colonoscopy; and**
- **Study III had two sites that videotaped the colonoscopy procedure; whereas, Study II had one site that videotaped the colonoscopy;**

This medical officer believes that EKGs should have been performed throughout the study because Visicol, a sodium phosphate product, has been associated with QTc prolongation in clinical trials and arrhythmias in post-marketing AE reporting.

Statistical Methods for the Co-Primary Efficacy Endpoints: According to the sponsor's statistical analysis plan, **twelve** comparisons will be performed using the Fisher's Exact test for the co-primary efficacy endpoints (percentage of responders that achieved an excellent or good score based on the Overall Colonic Content Scale and the percentage of responders that achieved an excellent or good score based on the Colonic Stool Scale):

1) Six comparisons: Visicol (arm A) compared to all six OsmoPrep arms (Arms B, C, D, E, F, and G) in the percentage of Colonic **Content** responders;
2) Six comparisons: Visicol compared to all six OsmoPrep arms in the percentage of Colonic **Stool** responders;

The sponsor will not perform multiplicity adjustments for the 12 cited comparisons of the co-primary efficacy endpoints.

Medical Reviewer's Comments: This is acceptable for a phase II study.

Statistical Populations in Study II: Study II had the three identical statistical populations (all assessed, per protocol, and safety population) as Study III. The all assessed population was used for the primary and secondary analyses.

6.4 Efficacy Findings

Disposition of Patients: Of 1055 patients who were scheduled to receive a colonoscopy in the two colonoscopy studies (Studies II and III), 749 patients were randomized to OsmoPrep and 306 patients were randomized to Visicol. Of the 749 patients who were randomized to OsmoPrep; 340, 341, and 68 patients were randomized to 60 grams (40 tablets), 48 grams (32 tablets), and 42 grams (28 tablets) of sodium phosphate, respectively. All of the 306 patients who were randomized to Visicol received 60 grams (40 tablets) of sodium phosphate. Table 16 highlights the disposition in the two OsmoPrep studies according to the three pre-specified populations (AAP, PP, and Safety).

Table 16: Patient disposition in the two OsmoPrep studies (Studies II and III)

Study	Treatment Group	Randomized	All Assessed Population	Per Protocol Population	Safety Population
		N (%)*	N (%)*	N (%)*	N (%)*
Study III	**Visicol 60 grams** (3 tablets split)[a]	272 (100)	235 (86)	213 (78)	238 (88)
	OsmoPrep 60 grams (4 tablets split)[b]	273 (100)	233 (85)	218 (80)	236 (86)
	OsmoPrep 48 grams (4 tablets split)[c]	271 (100)	236 (87)	217 (80)	239 (88)
	Total	**816 (100)**	**704 (86)**	**648 (79)**	**713 (87)**
Study II	**Visicol 60 grams** (3 tablets split)[a]	34 (100)	29 (85)	28 (82)	30 (88)
	OsmoPrep 60 grams (4 tablets split)[b]	34 (100)	29 (85)	25 (74)	29 (85)
	OsmoPrep 48 grams (4 tablets split)[c]	36 (100)	33 (92)	30 (83)	33 (92)
	OsmoPrep 60 grams (3 tablets split)[d]	33 (100)	32 (97)	28 (85)	32 (97)
	OsmoPrep 48 grams (all tablets in PM)[e]	34 (100)	30 (88)	29 (85)	30 (88)
	OsmoPrep 42 grams (all tablets in PM)[f]	34 (100)	32 (94)	30 (88)	33 (97)
	OsmoPrep	34 (100)	29 (85)	22 (65)	31 (91)

	42 grams (4 tablets split)[g]				
	Total	239 (100)	214 (90)	192 (80)	218 (91)
Total in Studies II and III		**1055 (100)**	**918 (87)**	**840 (80)**	**931 (88)**

* % is the percentage of the randomized population
a Visicol 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
b OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 20 tablets.
c OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 12 tablets.
d OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
e OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 10 PM the evening before colonoscopy, 4 tablets every 15 minutes until 12 tablets.
f OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 9 PM the evening before colonoscopy, 4 tablets every 15 minutes until 8 tablets.
g OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 8 tablets.
Reference: ISS, Section 2.2.1, Tables 4 and 5, Pages 28-30

Of the 239 randomized patients in Study II, 25 (10%) were discontinued from the study. Of the 25 patients who discontinued study drug, 21 (84%) patients did not receive study drug. Of the 21 patients did not receive study drug, 7 (33%) had exclusionary screening laboratory results, 5 (24%) were discontinued due to investigator decision, 5 (24%) had scheduling conflicts and/or family emergencies, 2 (10%) patients withdrew consent, and 2 (10%) patients discontinued because of intercurrent illness. Of the 4 patients who did receive the study drug and discontinued from the study, only 1 patient (who received 42 grams of OsmoPrep) discontinued due to a probable drug-related AE (vomiting) and the other 3 patients discontinued because of the following reasons: patient decision, noncompliance with study medication, and noncompliance with the protocol.

Of the 816 randomized patients in Study III, 110 (13%) were discontinued from the study. Of the 110 patients who discontinued study drug, 103 (94%) patients did not receive study drug. Of the 103 patients who did not receive study drug, 50 (49%) had exclusionary screening laboratory results; 28 (27%) had withdrew consent; 20 (19%) had scheduling conflicts, exclusionary medication, or lack of insurance coverage; 3 (3%) had intercurrent illness, 1 (1%) had entry violation, and 1 (1%) discontinued due to investigator decision. Of the 7 patients who did receive the study drug and discontinued from the study, 1 patient (who received 60 grams of OsmoPrep) discontinued due to an probable drug-related AE (vomiting) and 6 patients discontinued because of the following reasons: family emergency, unable to swallow pills, investigator decision, early termination of colonoscopy due to rectal pain, and two patients had exclusionary screening lab tests.

Efficacy Results

Pre-Specified Primary Efficacy Endpoint for Study III: In Study III, the pre-specified primary efficacy endpoint was the response rate to bowel cleansing. A patient was considered to be a responder if the Overall Colon Cleansing was rated by the **colonoscopist** as excellent (1) or good (2) according to a 4-point Colonic Content Scale (see Table 7).

The Visicol, OsmoPrep 60 gram, and OsmoPrep 48 gram treatment groups had 94.5%, 97.0%, and 95.3% responders in the Overall Bowel Colon Content Cleansing Scale, respectively. Accounting for the two statistical comparisons, the 60 gram OsmoPrep group was statistically non-inferior compared to the placebo group for the primary efficacy endpoint and the 48 gram OsmoPrep group was statistically non-inferior compared to the placebo group for the primary efficacy endpoint. Please see Table 17 for the results of the primary efficacy endpoint in Study III.

Table 17: Patients with excellent or good Overall Colon Content Cleansing (primary efficacy endpoint) in the AAP* in Study III

	Responder n (%)	Non-Responder n (%)	Difference in Response Rate	Lower bound of the one-sided 97.5% confidence interval % (p-value)
Visicol 60 grams (n=235)	222 (94.5)	13 (5.5)		
OsmoPrep 60 grams (n=233)	226 (97.0)	7 (3.0)	2.5%	-1.0% (< 0.0001)
OsmoPrep 48 grams (n=236)	225 (95.3)	11 (4.7)	0.8%	-2.8% (< 0.0001)

* AAP = all assessed population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy).
The primary efficacy endpoint was response rate to treatment. A patient was considered to be a responder if overall colon cleansing was rated by the colonoscopist as excellent (1) or good (2) according to a 4-point **Colonic Content** Scale (see Table 7). A patient was considered a non-responder if their Overall Colon Cleansing Score was rated by the colonoscopist as fair (3) or inadequate (4). **Colonic contents** were defined as all liquid, semisolid, and solid material in the lumen of the colon, seen during colonoscopy.
Reference: Final Report Study III, Section 11.1, Table 11.1-1, Page 56.

Medical Reviewer's Comments: In Study III, all three treatment groups had excellent responses in the primary efficacy endpoint. Responses ranged from 94.5% to 97%. However, as stated in section 6.1.2 (General Discussion of Endpoints) of this review, this medical officer believes that the primary efficacy responder analysis was not optimal in the determination of the efficacy of the study treatments because Likert responses 2 and 3 in the primary efficacy assessment can not be distinguished clinically from one another. Thus, medical officer recommends redefining a responder (the first exploratory analysis) as a patient who achieves an excellent response (1) only on the 4-point Colon Content Scale. Alternatively, a responder (the second exploratory analysis) could be defined as a patient who achieves a (1), (2), or (3) on the four-point Colonic Content Scale. Thus, responders are patients who have > 90% of mucosa seen in their colons.

Medical Reviewer's First Exploratory Analysis for Study III: Responders are defined as patients who achieve an excellent (1) and non-responders are patients who achieve a good (2), fair (3), or inadequate (4) on the 4-point Colon Content Grading Scale (see Table 7). In this exploratory analysis, 51%, 73%, and 76% of patients in the Visicol, OsmoPrep 60 gram, and OsmoPrep 48 gram treatment groups were responders, respectively (see Table 18). The two OsmoPrep dosage regimens appear to have similar — if not better — efficacy than the approved Visicol dosage regimen. This exploratory endpoint supports the efficacy of both doses of OsmoPrep as bowel cleansing preparations.

Table 18: First exploratory analysis: Patients with an excellent Overall Colon Content Cleansing in the AAP* in Study III

	1 (excellent) n (%)	2 (good) n (%)	3 (fair) n (%)	4 (inadequate) n (%)
Visicol 60 grams (n=235)	120 (51)	102 (43)	13 (6)	0 (0)
OsmoPrep 60 grams (n=233)	170 (73)	56 (24)	5 (2)	2 (1)
OsmoPrep 48 grams (n=236)	180 (76)	45 (19)	7 (3)	4 (2)

* AAP = All Assessed Population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy).
Reference: Adapted from Final Report Study III, Section 11.2.2, Table 11.2-2, Page 59.

Medical Reviewer's Second Exploratory Analysis for Study III: Responders are defined as patients who achieve an excellent (1), good (2), or fair (3) and non-responders are patients who achieve inadequate (4) on the 4-point Colon Content Grading Scale (see Table 19 for the results). In this second exploratory analysis, 100%, 99%, and 98% of patients in the Visicol, OsmoPrep 60 gram, and OsmoPrep 48 gram treatment groups were responders, respectively. The two OsmoPrep doses appear to have similar efficacy as the approved Visicol regimen in bowel cleansing. This second exploratory endpoint supports the efficacy of both doses of OsmoPrep as bowel cleansing preparations.

Table 19: Second exploratory analysis: Patients with an excellent, good, or fair Overall Colon Content Cleansing in the AAP* in Study III

	1, 2, or 3 (Responders) n (%)	1 (excellent) n (%)	2 (good) n (%)	3 (fair) n (%)	4 (inadequate) n (%)
Visicol 60 grams (n=235)	123 (100)	120 (51)	102 (43)	13 (6)	0 (0)
OsmoPrep 60 grams (n=233)	231 (99)	170 (73)	56 (24)	5 (2)	2 (1)
OsmoPrep 48 grams (n=236)	232 (98)	180 (76)	45 (19)	7 (3)	4 (2)

* AAP = All Assessed Population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy).
Reference: Adapted from Final Report Study III, Section 11.2.2, Table 11.2-2, Page 59.

Mean Overall Colon Cleansing Score - Important Secondary Efficacy Endpoint for Study III: The mean score of the 4-point (1-4) Overall Colon Cleansing Score was an important secondary endpoint in Study III (see Table 20 for the results).

Table 20: Secondary Endpoint: Mean Overall Cleansing Score in the AAP* in Study III

	1 (excellent) n (%)	2 (good) n (%)	3 (fair) n (%)	4 (inadequate) n (%)	Mean Score (SD)
Visicol 60 grams (n=235)	120 (51)	102 (43)	13 (6)	0 (0)	1.54 (0.6)
OsmoPrep 60 grams (n=233)	170 (73)	56 (24)	5 (2)	2 (1)	1.31 (0.56)
OsmoPrep 48 grams (n=236)	180 (76)	45 (19)	7 (3)	4 (2)	1.30 (0.61)

* AAP = All Assessed Population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy).
Reference: Adapted from Final Report Study III, Section 11.2.2, Table 11.2-2, Page 59.

Medical Reviewer's Comments: The 60 gram and 48 OsmoPrep dose regimens were numerically better than the Visicol regimen in mean overall cleansing score. The two OsmoPrep regimens had similar efficacy response for this endpoint. This secondary endpoint represents one of 16 pre-specified secondary endpoints in Study III. Because no multiplicity adjustments were pre-

specified, this secondary endpoint can be supportive evidence of the efficacy of OsmoPrep compared to Visicol in bowel cleansing.

Effective Ascending Colon Cleansing - Important Secondary Efficacy Endpoint for Study III: An important secondary endpoint was a responder analysis of the Ascending Colon Cleansing. Responders were patients who were graded as having an excellent (1) or good (2) score in the Ascending Colon by their colonoscopist. Non-responders were patients who were graded fair (3) or inadequate (4) on their Ascending Colon cleansing. This 4-point assessment scale was identical to the Overall Colon Content Cleansing Scale (see Table 21 for the results).

Table 21: Secondary Endpoint: Patients with excellent or good Ascending Colon Cleansing in the AAP* in Study III

	1 or 2 Responders n (%)	1 (excellent) n (%)	2 (good) n (%)	3 (fair) n (%)	4 (inadequate) n (%)
Visicol 60 grams (n=235)	208 (88)	123 (52)	85 (36)	27 (11)	0 (0)
OsmoPrep 60 grams (n=233)	220 (94)	173 (74)	47 (20)	10 (4)	0 (0)
OsmoPrep 48 grams (n=236)	220 (93)	177 (75)	43 (18)	12 (5)	3 (1)

* AAP = All Assessed Population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy).
Reference: Adapted from Final Report Study III, Section 11.2.3, Table 11.2-3, Page 61.

Medical Reviewer's Comments: The 60 gram and 48 OsmoPrep dose regimens were numerically better than the Visicol regimen in the proportion of responders in the Ascending Colon Cleansing Scale. The two OsmoPrep regimens had similar efficacy response for this endpoint. This endpoint is supportive of the efficacy of both OsmoPrep regimens in bowel preparation.

Mean Ascending Colon Cleansing Score - Important Secondary Efficacy Endpoint for Study III: Another important secondary efficacy endpoint was the mean Ascending Colon Cleansing Score (see Table 22).

Table 22: Secondary Endpoint: Mean Ascending Colon Cleansing Score in the AAP* in Study III

	1 (excellent) n (%)	2 (good) n (%)	3 (fair) n (%)	4 (inadequate) n (%)	Mean Score (SD)
Visicol 60 grams (n=235)	123 (52)	85 (36)	27 (11)	0 (0)	1.59 (0.69)
OsmoPrep 60 grams (n=233)	173 (74)	47 (20)	10 (4)	0 (0)	1.29 (0.54)
OsmoPrep 48 grams (n=236)	177 (75)	43 (18)	12 (5)	3 (1)	1.40 (0.64)

* AAP = All Assessed Population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy).
Scores ranged from 1 (excellent) to 4 (inadequate)
Reference: Adapted from Final Report Study III, Section 11.2.3, Table 11.2-3, Page 61.

Medical Reviewer's Comments: The 60 gram and 48 OsmoPrep treatment groups had numerically superior mean Ascending Colon Cleansing Scores compared to the Visicol group. These results support the efficacy of both OsmoPrep doses compared to Visicol for colon cleansing.

Pre-Specified Co-Primary Efficacy Endpoints for Study II: In Study II, the pre-specified co-primary efficacy endpoints were the response rates to bowel cleansing in the Overall Colon **Content** Cleansing Scale and in the Overall Colon **Stool** Cleansing Scale. For the 4-point Overall Colon **Content** Cleansing Scale — identical to the primary efficacy endpoint in Study III — a patient was considered to be a responder if overall colon cleansing was rated by the colonoscopist as excellent (1) or good (2). Similarly, for the 4-point Colon **Stool** Cleansing Scale a patient was considered to be a responder if overall colon cleansing was rated by the colonoscopist as excellent (1) or good (2). Since Study II had 6 pre-specified comparisons (each of 6 OsmoPrep dosing regimens were compared to the one Visicol regimen), 12 statistical analyses were performed for the co-primary efficacy endpoints (see Table 23).

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Table 23: The co-primary efficacy endpoints (percentage of responders) in the AAP* in Study II

	Visicol® (60g) 40 Tabs	INKP-102 Treatment Groups						All patients
		40 Tabs (60g)		32 Tabs (48g)		28 Tabs (42g)		
	A	B	C	D	E	F	G	
	3 tabs split (N=29)	3 tabs split (N=32)	4 tabs split (N=29)	4 tabs evening (N=30)	4 tabs split (N=33)	4 tabs evening (N=32)	4 tabs split (N=29)	(N=214)
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)
Colonic content								
Responder	25 (86)	31 (97)	29 (100)	27 (90)	32 (97)	23 (72)	26 (90)	193 (90)
Nonresponder	4 (14)	1 (3)	0 (0)	3 (10)	1 (3)	9 (28)	3 (10)	21 (10)
P-value		0.1816	0.1120	0.7065	0.1762	0.2192	>0.9999	
Stool								
Responder	26 (90)	31 (97)	29 (100)	26 (87)	33 (100)	24 (75)	26 (90)	195 (91)
Nonresponder	3 (10)	1 (3)	0 (0)	4 (13)	0 (0)	8 (25)	3 (10)	19 (9)
P-value		0.3385	0.2368	>0.9999	0.0966	0.1884	>0.9999	

Visicol was compared to 6 OsmoPrep groups. The p-values were determined by the Fisher's Exact Test.
The first co-primary efficacy endpoint was response rate to treatment. A patient was considered to be a responder if Overall Colon Cleansing was rated by the colonoscopist as excellent (1) or good (2) according to a 4-point **Colonic Content** Scale (see Table 7). A patient was considered a non-responder if their overall colon cleansing score was rated by the colonoscopist as fair (3) or inadequate (4). **Colonic contents** were defined as all liquid, semisolid, and solid material in the lumen of the colon, seen during colonoscopy.
The second co-primary efficacy endpoint was response rate to treatment. A patient was considered to be a responder if the Overall Colon Cleansing was rated by the colonoscopist as excellent (1) or good (2) according to a 4-point Colonic **Stool** Scale (see Table 8). A patient was considered a non-responder if their overall colon cleansing score was rated by the colonoscopist as fair (3) or inadequate (4).
* AAP = All Assessed Population (Patients who ingested at least one sodium phophate tablet and had a colonoscopy);
INKP-102 = OsmoPrep
Reference: Final Report Study II, Section 11.1, Table 11.1-1, Page 45.

Medical Reviewer's Comments: Since no multiplicity adjustments were pre-specified for the 12 analyses of the co-primary efficacy endpoints and each treatment group had a small number of patients (about 30 patients per treatment group), Study II should be used as supportive — not primary — evidence for the efficacy of OsmoPrep in bowel cleansing.

In Study II, the efficacy results for the stool and the colon content cleansing for each study treatment were very similar.

In Study II, the four OsmoPrep split dosing regimens had greater numerical efficacy (in both the Stool and Colon Content Cleansing) then the two OsmoPrep evening-only dosing regimens. In the four OsmoPrep split dosing regimens, the higher OsmoPrep doses (60 and 48 grams) had greater numerical efficacy (in both the Stool and Colon Content Cleansing) than the lowest OsmoPrep dose (42 grams). This dose response supports the efficacy of OsmoPrep.

For the sponsor's phase 3 trial (Study III), the sponsor chose two of the most efficacious regimens (OsmoPrep dosing regimens C and E used in Study II). Patients taking OsmoPrep regimens C and E in Study II had a response rate of 100% and 97% in the Colon Content Cleansing Scale, respectively. Also, patients taking OsmoPrep regimens C and E in Study II both had a response rate of 100% in the Colon Stool Cleansing Scale. From an efficacy standpoint, the sponsor chose the most appropriate OsmoPrep dosing regimens for Study III.

Given the 12 statistical comparisons for the primary efficacy endpoint and the lack of multiplicity adjustments, formal statistical analyses cannot be performed regarding the efficacy of the six OsmoPrep regimens compared to the Visicol regimen. Three OsmoPrep dosing regimens (B, C, and E) had numerical improvements compared to the Visicol regimen in both stool and colon content cleansing. However, the Visicol regimen had numerical improvement compared to the 42 gram OsmoPrep evening-only dosing regimen (Arm F).

6.5 Clinical Microbiology

A clinical microbiology review is not applicable.

6.6 Efficacy Conclusions

In Study II, the 60 gram OsmoPrep split dose (Arm C) and the 48 gram OsmoPrep split dose (Arm E) were two of the best responders in the co-primary efficacy endpoints [the frequency of patients who achieved an excellent (1) score or a good (2) score on the 4-point Overall Colon Contents Cleansing Scale and the 4-point Overall Colon Stool Cleansing Scale]. In the 60 gram Visicol, 60 gram OsmoPrep, and the 48-gram OsmoPrep groups, 86%, 100%, and 97% of patients were responders, respectively, in the Overall Colon Contents Cleansing Scale. A similar frequency of responders in each treatment group occurred in the other co-primary efficacy endpoint (the Overall Colon Stool Cleansing Scale). The two cited OsmoPrep dosing regimens were selected for the phase 3 study (Study III) because they were two of the greatest responders in the phase 2 study (Study II).

In Study III, the 60 gram Visicol, 60 gram OsmoPrep, and the 48-gram OsmoPrep groups had response rates of 95%, 97%, and 95%, respectively, in the Overall Colon Contents Cleansing Scale (the primary efficacy endpoint). The two OsmoPrep dosing regimens were non-inferior to the Visicol dosing regimen in the primary efficacy endpoint.

All three important secondary endpoints in Study III demonstrated that both OsmoPrep dosing regimens were numerically superior to the Visicol dosing regimen (the active control). Furthermore, the two FDA post-hoc efficacy analyses demonstrated that both OsmoPrep dosing regimens were numerically superior or non-inferior to the Visicol dosing regimen.

In summary, the clinical data from the two well-controlled OsmoPrep studies support the efficacy of the sponsor's proposed 48 gram OsmoPrep dosing regimen for colon cleansing prior to a colonoscopy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

In all of the studies in this NDA (Studies I, II, and III), there were no deaths in any patient or subject.

7.1.2 Other Serious Adverse Events

In the entire OsmoPrep safety population (Studies II and III), two patients had a SAE. Since OsmoPrep is an investigational drug in the United States and has never been approved in any country, OsmoPrep exposure pertains to the trials submitted in this NDA. Both of patients who experienced an SAE received OsmoPrep 60 grams in Study III (there were no SAEs in Study II). One patient experienced ischemic colitis and the other patient experienced bloating (see Table 24 for the SAE narratives). Thus, no patient who received OsmoPrep 48 grams, OsmoPrep 42 grams, Visicol, or placebo experienced an SAE in Studies II or III.

Table 24: Narratives of SAEs in Studies II and III

Study/ Patient ID#/ Study Drug	SAE	Medical History
In Study III, Patient 1702 received 60 grams of OsmoPrep	Ischemic Colitis	66 year old male (with a past medical history of CABG in 1986; heart transplant in [redacted] for progressive CAD, CHF, and ischemic cardiomyopathy; HTN, hyperlipidemia, and hypothyroidism and taking Enalapril, CellCept, Gengraf, and Levoxyl) was scheduled for a colonoscopy because of an episode of melena, rectal bleeding, and diarrhea in June 2004. After randomization and finding no baseline laboratory abnormalities, he took 20 tablets of study medication between 6 to 7 PM and took 2.9 liters of clear liquids on [redacted] (the night before the colonoscopy). At 7 PM he began to have **abdominal cramping, diaphoresis, rectal bleeding, and diarrhea**. On the day of his colonoscopy ([redacted]), he took 60 mL of water, but did not take his second dose of study medication. At the Endoscopy Unit, he was noted to be **dehydrated**, had **symptomatic postural hypotension**, and had **hypokalemia** (3.2 mEq/L). He received a bolus of 750 mL of Normal Saline and had a colonoscopy at 5:15 PM. Colonoscopy showed nonbleeding internal hemorrhoids, sigmoid diverticula, a nonbleeding 2 cm polyp at 20 cm (tubular adenoma), a nonbleeding 3 mm polyp, and 15 to 20 ulcers at 40 to 60 cm (diagnosed as ischemic colitis). One ulcer was 3 cm and another 7 cm in diameter. The patient was hospitalized for one night for fluid and potassium repletion and the patients symptoms resolved as an outpatient 5 days after discharge [redacted] The investigator labeled this SAE definitely related to the study medication. The sponsor thought that the following factors contributed to the ischemic colitis: underlying vascular disease (CAD, HTN, and

		hyperlipidemia), dehydration (diarrhea, bleeding, and poor fluid intake), hypotension, and the use of an ACE inhibitor.
In Study III, Patient 2313 received 60 grams of OsmoPrep	Bloating	45 year old female (with a family history of colon cancer, a medical history of migraine headaches, and a surgical history of two Caesarean sections, ventral hernia repair, and tubal ligation) was scheduled for a screening colonoscopy. After randomization and finding no baseline laboratory abnormalities, she took 20 tablets of study medication after 6:15 PM on [redacted] the night before the colonoscopy) and took 20 tablets of study medication before 7 AM on [redacted] the day of the colonoscopy). She developed **mild nausea** on [redacted] efore the colonoscopy. The colonoscopy showed diverticulosis and angulation secondary to adhesions. After the colonoscopy, she experienced **severe bloating** and a small amount of **rectal bleeding** that required an Emergency Room visit and one day of hospitalization. She received intravenous fluids and abdominal X-ray showed an ileus. After her symptoms resolved on [redacted] she was discharged. The investigator felt that her symptoms were not related to the study medication.

Reference: Adapted from Study III, Section 14.3.3.1, Page 400-402

Medical Reviewer's Comments: **In all of the OsmoPrep trials (Studies II and III), 2 (0.67%), 0 (0%), 0 (0%), and 0 (0%) patients experienced a SAE in the OsmoPrep 60 gram, OsmoPrep 48 gram, OsmoPrep 42 gram, and Visicol treatment groups, respectively.**

Patient 1702 had abdominal cramping, diaphoresis, rectal bleeding, and diarrhea; was diagnosed with dehydration, hypokalemia, and ischemic colitis; and required hospitalization. Thus patient 1702 clearly had a SAE. Patient 1702's dehydration was likely due to OsmoPrep; however, dehydration is not specific for this bowel preparation. All bowel cleansing agents can cause diarrhea and can produce dehydration. Patient 1702's hypokalemia was likely due to OsmoPrep since a significant percentage of patients receiving sodium phosphate preparations develop hypokalemia.

Patient 1702's ischemic colitis is not clearly due to OsmoPrep treatment. Patient 1702 had many risk factors for ischemic colitis including vascular disease (given his history of CAD, ischemic cardiomyopathy, HTN, and hyperlipidemia). Additionally, his ulcers occurred near the splenic flexure, a watershed region of the colon likely to be affected by hypotension. Patient 1702's blood pressure medication (enalapril), diarrhea, and rectal bleeding may have contributed to his hypotension. Thus, this medical officer believes that any bowel preparation could have contributed to his ischemic colitis.

Patient 2313 developed mild nausea, severe bloating, a small amount of rectal bleeding, and a possible ileus which required hospitalization. This medical officer believes that any bowel preparation could contribute to nausea and bloating. Additionally, bloating and rectal bleeding may have been a complication of the colonoscopy because air is inserted into the colon. Perhaps the patient's history of multiple abdominal surgeries contributed to adhesions of the small intestine or colon which contributed to the ileus pattern on X-ray. This medical officer believes that these SAEs may have not been specifically related to OsmoPrep.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of the 713 patients (in the safety population) in Study III, a total of 11 (1.5%) patients discontinued study medication including 4 (0.6%) patients who remained in the study and 7 (1.0%) patients who were discontinued from the study. Of the 4 patients who remained in the study, all 4 had AEs (see Table 25 for the complete patient narratives). Of the 7 patients who were discontinued from the study, 2 patients had AEs, 1 patient was lost to follow up, 2 patients had exclusionary screening tests, and 2 patients had other reasons (see Table 25 for the patient narratives).

Table 25: Narratives of patients who discontinued study medication in Study III

	Patient Number	Study Treatment	Reason for Stopping Study Treatment	Narrative
1	2428	OsmoPrep 60 grams	AEs; Remained in Study	49 year old female (with a past medical history of sinusitis, hypercholesterolemia, mitral valve prolapse, GERD, hypothyroidism, fibromyalgia, anxiety, migraines, insomnia, bladder spasms, and hysterectomy and taking dicyclomine, sucralfate, Nexium, Urispas, Zyrtec, Lipitor, metoprolol, levothyroxine, Cymbalta, estradiol, and trazodone) who started her study medication at 6 PM on November 17, 2004. She took 20 pills at night and developed **flushing, rash, mild abdominal pain, bloating, blurred vision, nausea, and vomiting**. She took 4 pills of study medication on the morning of the colonoscopy. Physical exam showed a macular erythematous rash on the chest and back which resolved on November 18, 2004. The investigator felt that these events were all possibly related to the study medication.
2	2407	OsmoPrep 60 grams	AEs; Remained in Study	37 year old male (with past medical history of myalgias taking no medications) took 20 tablets of study medication beginning at 6 PM on October 7, 2004. Starting at 9 AM on October 8, 2004 (the day of the colonoscopy), he took 11 tablets of study medication by 9:45 AM. He developed **severe nausea and vomiting** and vomited his last 8 tablets. All of these AEs resolved on October 8, 2004. The investigator stated that these AEs were definitely related to study medication.
3	2120	OsmoPrep 60 grams	AEs; Remained in Study	24 year old female (with a past medical history of GERD taking Protonix and BCPs) referred for a colonoscopy due to rectal bleeding; began study medication at 6 PM on November 17, 2004 and took 20 pills by 7:30 PM (she was given an incorrect dosing regimen of 3 pills every 15 minutes instead of 4 pills every 15 minutes). She developed **severe nausea and vomiting** and **mild abdominal pain and bloating**. She did not take any more study medication on the colonoscopy day. Her symptoms resolved on November 18, 2004. The investigator

				characterized the nausea and vomiting as definitely related and the abdominal pain and bloating as possibly related to the study medication.
4	1702	OsmoPrep 60 grams	AEs; Remained in Study	See narrative in the SAE Table 24
5	2920	OsmoPrep 60 grams	AEs; Withdrew from Study	39 year old female (with past medical history of seasonal allergies, GERD, anxiety, chronic cough, and tubal ligation and taking Aciphex, Advil, and Tavist-D) was referred for a colonoscopy because of rectal bleeding. She started 20 pills of the study medication at 6:00 PM on October 31, 2004, the night before the colonoscopy. That evening she developed **severe vomiting** which resolved November 1, 2004. The investigator thought that the vomiting was drug-related. Also she developed **mild epigastric pain** on November 2, 2004. She did not have the colonoscopy.
6	0325	Visicol	AE; Withdrew from Study	**Rectal pain** during colonoscopy. Investigator felt this event was not related to the study medication.
7	3022	Visicol	Lost to follow-up; Withdrew from Study	Lost to follow-up because of a family emergency. Did not have the colonoscopy.
8	0329	Visicol	Exclusionary baseline test; Withdrew from Study	Exclusionary screening lab results (baseline labs showed increased magnesium levels). This screening failure was not communicated to the patient, so the patient took 20 pills of study medication on the day prior to the colonoscopy.
9	1242	OsmoPrep 60 grams	Investigator decision; Withdrew from Study	Investigator decision to withdraw the patient because the patient drank liquid one hour prior to the colonoscopy.
10	3109	OsmoPrep 48 grams	Patient withdrew consent; Withdrew from Study	Patient withdrew consent because the patient was not able to swallow pills.
11	0343	OsmoPrep 48 grams	Exclusionary baseline test; Withdrew from Study	Exclusionary screening lab results (baseline labs showed hypokalemia). The patient took 4 pills of study medication before listening to the patient's voicemail that instructed the patient not to take study medication due to the abnormal lab test. After hearing the voicemail, the patient did not take additional study medication.

Reference: Adapted from Study III, Section 14.3.3.2, Pages 402-404

Medical Reviewer's Comments: In Study III, this medical officer believes that five patients (Patients 2428, 2407, 2120, 2920, and 1702) discontinued their study medication because of study drug-related AEs. Patients received the OsmoPrep 60 gram dose in all of these cases. Of

these five cases, four patients had vomiting (Patients 2428, 2407, 2120, and 2920) and one patient (Patient 1702) had abdominal cramping, diarrhea, dehydration, hypotension, and hypokalemia. In these five cases, all of the AEs were temporally related to the timing of study drug administration. This medical officer believes that the ischemic colitis that occurred in Patient 1702 was probably was due to hypovolemia and/or underlying vascular disease. The hypovolemia would likely have occurred with the use of any bowel preparation. This medical officer does not think that OsmoPrep is more likely to cause ischemic colitis, compared to other approved bowel preparations.

This medical officer believes that the AE that occurred in Patient 0325 was related to the colonoscopy procedure; not to the study drug (Visicol).

Of the 218 patients (in the safety population) in Study II, a total of 5 (2.3%) patients discontinued study medication including 1 (0.5%) patient who remained in the study and 4 (1.8%) patients who were discontinued from the study. The patient who remained in the study and discontinued study medication had an AE (see Table 26). Of the 4 patients who discontinued from the study, 1 patient discontinued due to an AE and 3 patients discontinued because of the following reasons: patient decision, noncompliance with study medication, and noncompliance with the protocol.

Table 26: Narratives of patients who discontinued study medication in Study II

	Patient Number	Study Treatment	Reason for Stopping Study Treatment	Narrative
1	0234	Evening-only OsmoPrep (42 grams)	AE; Remained in Study	56 year old female (with a past medical history of GERD) took 20 tablets of study medication and had a **GERD exacerbation**. She completed the colonoscopy and the study.
2	0213	Evening-only OsmoPrep (42 grams)	AE; Withdrew from Study	33 year old female (with no significant past medical history) experienced **abdominal pain, nausea, and vomiting** on the evening prior to her colonoscopy (March 25, 2004). Her symptoms resolved on March 26, 2004. She did not have the colonoscopy.
3	0418	Split doses OsmoPrep (42 grams)	Withdrew from Study	Patient decision
4	0547	Visicol (60 grams)	Withdrew from Study	Investigator decision because of noncompliance with study medication (patient only took 18 of 40 required tablets)
5	0544	Split doses OsmoPrep (42 grams)	Withdrew from Study	Investigator decision because of noncompliance with the study protocol (the patient ate breakfast on the morning of the scheduled colonoscopy)

Reference: Adapted from Study II, Section 12.3, Page 60

Medical Reviewer's Comments: In Study II, this medical officer believes that two patients (Patients 0234 and 0213) discontinued their study medication because of drug-related AEs. Both patients received the evening-only OsmoPrep 42 gram dose. Of these two cases, one patient (Patient 0234) had a GERD exacerbation and one patient (Patient 0213) had abdominal pain, nausea, and vomiting. In these two cases, all of the AEs were temporally related to the timing of study drug administration. Since GERD exacerbation and vomiting are AEs that are common to other approved bowel preparations, this medical officer believes that OsmoPrep is not more likely to cause these AEs than other approved bowel preparations.

7.1.3.2 Adverse events associated with dropouts

Please see responses to Section 7.1.3.1.

7.1.3.3 Other significant adverse events

There are no other significant AEs.

7.1.4 Other Search Strategies

Please see Section 7.1.7 (Laboratory Findings) for a detailed review of the multiple electrolyte changes associated with OsmoPrep administration.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In Studies II and III, AEs were defined as any clinical illness, sign, or symptom that appeared or worsened during the study after study medication has been taken by the patient, whether or not the abnormality was believed by the investigator to be related to the study medication. Complications of colonoscopy or the bowel preparations (study treatments) were considered to be AEs, including, but not limited to, perforation and post-procedure bleeding. Laboratory abnormalities that were associated with a clinical AE were reported as AEs.

In Studies II and III, multiple events were not recorded as AEs. Diarrhea, an expected outcome of treatment with sodium phosphate tablets, was not captured as an AE unless it met the criteria for a SAE. Laboratory abnormalities (even severe laboratory abnormalities) that were not associated with a clinical AE were not reported as AEs.

In Study III, colonoscopy findings that led to follow-up treatment (including surgery) after the colonoscopy were not captured as AEs unless hospitalization was prolonged. In Study III only AEs that required hospitalization, an emergency room visit, or which precipitated a visit to a health care provider were recorded as AEs during the follow-up telephone call two weeks (± 3 days) after colonoscopy. Study II did not include a follow-up telephone call or a follow-up visit after the colonoscopy.

In Studies II and III, AEs were reported spontaneously by the patient or after non-leading questioning by the study coordinator during only one visit (on the day of the colonoscopy). AEs were reported if an abnormality was noted on physical exam during the colonoscopy visit. Additionally, four common GI AEs associated with purgative use (nausea, vomiting, abdominal pain, and bloating) were solicited on the Patient Questionnaire (completed by the patient just prior to the colonoscopy procedure).

Medical Reviewer's Comments: This medical officer believes that Studies II and III had suboptimal follow-up safety procedures. Neither Study II nor Study III had one follow-up safety visit post-colonoscopy. Sodium phosphate bowel preparation products including Visicol and OTC professionally-labeled OSPS have been associated with severe electrolyte abnormalities and serious complications of electrolyte abnormalities including arrhythmias, seizures, and acute renal failure from acute phosphate nephropathy. Over 40 post-marketing cases of acute renal failure (mostly due to acute phosphate nephropathy) have been associated with sodium phosphate bowel preparation use. Many of the patients who developed renal failure were diagnosed over two months after their bowel preparation use. Thus, the safety procedures for Studies II and III would not have picked up these electrolyte SAEs.

Unfortunately, most bowel preparation clinical studies submitted to the Agency have lacked optimal follow-up safety procedures. Most bowel preparations trials (including Studies II and III in this NDA) have lacked any post-colonoscopy safety visit. This medical officer believes that all future trials of bowel preparations should have better safety follow-up evaluations (e.g., a follow-up safety visit about 7 days after the colonoscopy).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Studies II and III used the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 7.0 nomenclature to classify AEs.

7.1.5.3 Incidence of common adverse events

Of the 713 patients in the safety population in Study III, 455 (64%) experienced at least one AE. The most common AEs were GI AEs. Of the 455 patients who experienced an AE, 442 (97.1%) experienced a GI AE. The most common AEs included abdominal distension (bloating), nausea, abdominal pain, and vomiting (see Table 27).

Table 27: Most common AEs (≥ 2% of patients in any treatment group) in descending frequency in the safety population in Study III

System Organ Class/ Preferred Term	Visicol 60 g; 40 tablets N=238	INKP-102 60 g; 40 tablets N=236	INKP-102 48 g; 32 tablets N=239	All patients (N=713)
	n (%)	n (%)	n (%)	n (%)
No. of patients with ≥1 AE	161 (68)	156 (66)	138 (58)	455 (64)
Gastrointestinal	157 (66)	152 (64)	133 (56)	442 (62)
Abdominal distention	101 (42)	93 (39)	73 (31)	267 (37)
Nausea	77 (32)	93 (39)	66 (28)	234 (33)
Abdominal pain	61 (26)	59 (25)	56 (23)	176 (25)
Vomiting	18 (8)	22 (9)	10 (4)	50 (7)
Nervous system	8 (3)	13 (6)	10 (4)	31 (4)
Headache	6 (3)	6 (3)	7 (3)	19 (3)
Dizziness	1 (< 1)	5 (2)	3 (1)	9 (1)

INKP-102 (OsmoPrep)
Reference: Study III, Section 12.2.1, Table 12.2-1, Page 72

Of the 218 patients in the safety population in Study II, 102 (47%) experienced at least one AE. The most common AEs were GI AEs. Of the 102 patients who experienced an AE, 99 (97%) experienced a GI AE. The most common AEs included abdominal distension (bloating), nausea, abdominal pain, and vomiting (see Table 28).

Table 28: Most common AEs (≥ 2% of patients in any treatment group) in descending frequency in the safety population in Study II

Category	Visicol (60g) 40 Tablets @3 Tabs Split (N=30)	INKP-102 (60g) 40 Tablets @3 Tabs Split (N=32)	INKP-102 (60g) 40 Tablets @4 Tabs Split (N=29)	INKP-102 (48g) 32 Tablets @4 Tabs Evening (N=30)	INKP-102 (48g) 32 Tablets @4 Tabs Split (N=33)	INKP-102 (42g) 28 Tablets @4 Tabs Evening (N=33)	INKP-102 (42g) 28 Tablets @4 Tabs Split (N=31)	All Patients (N=218)
ABDOMINAL DISTENSION	9 (30)	14 (44)	10 (34)	5 (17)	10 (30)	9 (27)	7 (23)	64 (29)
NAUSEA	6 (20)	8 (25)	6 (21)	5 (17)	6 (18)	10 (30)	9 (29)	50 (23)
ABDOMINAL PAIN	7 (23)	9 (28)	5 (17)	4 (13)	6 (18)	7 (21)	4 (13)	42 (19)
VOMITING	5 (17)	2 (6)	4 (14)	2 (7)	1 (3)	3 (9)	3 (10)	20 (9)
HEADACHE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	2 (< 1)
CONGENITAL CYSTIC KIDNEY DISEASE	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	1 (< 1)
DIZZINESS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (< 1)
DYSPEPSIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (< 1)
HYPOAESTHESIA	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)
PERIPHERAL COLDNESS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (< 1)
RASH	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (< 1)
UPPER RESPIRATORY TRACT INFECTION	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)

INKP-102 (OsmoPrep)
Reference: Study II, Table 9.2, Page 175

Medical Reviewer's Comments: Studies II and III had similar frequencies of the most common AEs (GI AEs). In Study III, the treatment groups (Visicol and OsmoPrep 60 grams)

that contained 60 grams of sodium phosphate had slightly higher frequencies of GI AEs compared to the treatment group (OsmoPrep 48 grams) that contained 48 grams of sodium phosphate. Since Study II had very small numbers of patients, it is difficult to compare the frequencies of AEs amongst the seven treatment groups.

The four most common AEs (abdominal distension, nausea, abdominal pain, and vomiting) in Studies II and III were most likely due to two reasons. First, all of these four specific GI AEs were solicited on the Patient Questionnaire to all the patients in Studies II and III; in contrast other AEs had to be spontaneously reported by patients. Secondly, these GI AEs are common to all bowel preparations.

Diarrhea was not one of the most common AEs reported because the sponsor did not categorize diarrhea as an AE. However, this medical officer recommends that this study procedure should be detailed in the OsmoPrep label. This medical officer believes that the sponsor's approach was reasonable since the sponsor established procedures to identify dehydration-related AEs including orthostatic hypotension measurements.

In Studies II and III, the OsmoPrep 48 gram split-dose was associated with a lower percentage of AEs than the approved Visicol regimen. Thus, the sponsor's proposed OsmoPrep dose appears to be as safe as the approved Visicol regimen.

7.1.5.4 Common adverse event tables

Please see Section 7.1.5.3 for the common AE tables in Studies II and III.

7.1.5.5 Identifying common and drug-related adverse events

Table 29 lists the most common drug-related AEs (≥ 1% of patients in the safety population) in descending frequency in Study III.

Table 29: Most common drug-related AEs (≥ 1% of patients in the safety population) in descending frequency in Study III

Preferred Term	Visicol 60 g (n=238) n (%)	OsmoPrep 60 g (n=236) n (%)	OsmoPrep 48 g (n=239) n (%)	All Treatments (n=713) n (%)
Abdominal Distention (Bloating)	91 (38)	83 (35)	66 (28)	240 (34)
Nausea	73 (31)	85 (36)	61 (26)	219 (31)
Abdominal Pain	54 (23)	53 (22)	53 (22)	160 (22)
Vomiting	16 (7)	20 (8)	10 (4)	46 (6)
Headache	4 (2)	3 (1)	6 (3)	13 (2)
Dizziness	1 (<1)	5 (2)	3 (1)	9 (1)

Reference: Adapted from Study III Final Study Report, Table 9.4, Page 244

Table 30 lists the most common drug-related AEs (≥ 1% of patients in the safety population) in descending frequency in Study II.

Table 30: Most common drug-related AEs (≥ 1% of patients in the safety population) in descending frequency in Study II

Preferred Term	Visicol 60 g[1] (n=30)	OsmoPrep 60 g[2] Split dose (3 pills) (n=32)	OsmoPrep 60 g[3] Split dose (4 pills) (n=29)	OsmoPrep 48 g[4] PM-only (n=30)	OsmoPrep 48 g[5] Split dose (n=33)	OsmoPrep 42 g[6] PM-only (n=33)	OsmoPrep 42 g[7] Split dose (n=31)	All Treatments (n=218)
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal Distention (Bloating)	9 (30)	14 (44)	10 (34)	5 (17)	9 (27)	9 (27)	7 (23)	63 (29)
Nausea	6 (20)	8 (25)	6 (21)	5 (17)	6 (18)	10 (30)	9 (29)	50 (23)
Abdominal Pain	7 (23)	9 (28)	5 (17)	4 (13)	5 (15)	7 (21)	4 (13)	41 (19)
Vomiting	4 (13)	2 (6)	4 (14)	2 (7)	1 (3)	3 (9)	3 (10)	19 (9)
Headache	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	2 (<1)
zziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (<1)

Visicol 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
2 OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
3 OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 20 tablets.
4 OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 10 PM the evening before colonoscopy, 4 tablets every 15 minutes until 12 tablets.
5 OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 12 tablets.
6 OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 9 PM the evening before colonoscopy, 4 tablets every 15 minutes until 8 tablets.
7 OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 8 tablets.
Reference: Adapted from Study II Final Study Report, Table 9.4, Page 184

Medical Reviewer's Comments: Studies II and III had similar frequencies of the most common drug-related AEs (abdominal distension, nausea, abdominal pain, and vomiting). Common drug-related AEs were similar to the common AEs (see Tables 29 and 30)

This medical officer agrees that the four GI symptoms (abdominal distension, nausea, abdominal pain, and vomiting) were likely drug-related. However, these symptoms are very likely to occur with all approved bowel preparations.

7.1.5.6 Additional analyses and explorations

Medical Reviewer's Comments: In the combined safety database, the two treatment groups (Visicol and OsmoPrep 60 grams) that contained 60 grams of sodium phosphate had slightly higher frequencies of GI drug-related AEs compared to the OsmoPrep 48 gram treatment group (see Tables 29 and 30). Thus, the sponsor's proposed OsmoPrep dose appears to be as safe as the approved Visicol regimen.

7.1.6 Less Common Adverse Events

Since this NDA has a relatively small safety database, this medical officer will not analyze less common AEs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Patients in Studies II and III had the following baseline and colonoscopy-day laboratory tests: serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphate, and magnesium), BUN, and creatinine. For women of childbearing potential (including women with a prior tubal ligation who were still menstruating), a serum pregnancy test was performed (serum HCG).

All laboratory abnormalities (even severe abnormalities) were not routinely reported as AEs. Only if laboratory abnormalities were associated with clinical events were they classified as AEs.

Medical Reviewer's Comments: Studies II and III did not include the following routine laboratory tests: a complete blood count (CBC), liver enzyme tests (such as alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, and alkaline phosphatase), or coagulation tests (such as INR and PTT). Without performing liver enzyme tests and CBCs, it is difficult to assess if there is drug-related hepatitis, cholestatic disease, anemia, thrombocytosis, thrombocytopenia, or leukopenia. Additionally, these laboratory tests are important to help determine if there are any drug-drug interactions. This medical officer believes that the sponsor should have performed these routine baseline and treatment period laboratory tests.

Additionally, Studies II and III did not perform any laboratory tests after the colonoscopy was performed. Since there have been over 40 post-marketing cases of renal failure (mostly due to acute phosphate nephropathy) associated with sodium phosphate bowel preparations and renal failure was diagnosed frequently weeks after administration of the bowel preparations, this medical officer believes that the sponsor should have performed laboratory tests after the colonoscopy. Post-colonoscopy tests should have included electrolytes, BUN, creatinine, phosphate, calcium, and potassium. This medical officer believes that these tests should have been performed several days after the colonoscopy.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This medical officer selected Studies II and III to compare laboratory values between the treatment groups because these were the only two controlled studies submitted in this NDA, they contained the proposed patient population (patients who will undergo elective colonoscopy), and included the proposed OsmoPrep dosing regimen. Furthermore, both Studies II and III had an active control treatment group (Visicol), an approved bowel preparation.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Tables 31 and 32 display the central tendencies of electrolyte measurements in the safety populations in Studies III and II, respectively.

Table 31: Central tendencies of electrolyte measurements in the safety population in Study III

Laboratory Test	Measurement Day	Visicol 60 g (n=235) n (%)	OsmoPrep 60 g (n=233) n (%)	OsmoPrep 48 g (n=236) n (%)
Mean Phosphate level (mg/dL)	Screening	3.5	3.5	3.6
	Colonoscopy Day	7.6	7.9	7.1
	Mean Change	4.0	4.4	3.5
Mean Sodium level (mEq/L)	Screening	141	141	141
	Colonoscopy Day	143	144	143
	Mean Change	2	3	2
Mean Potassium level (mEq/L)	Screening	4.4	4.3	4.3
	Colonoscopy Day	3.7	3.7	3.7
	Mean Change	-0.7	-0.6	-0.6
Mean Calcium level (mg/dL)	Screening	9.8	9.7	9.7
	Colonoscopy Day	9.2	9.3	9.2
	Mean Change	-0.6	-0.47	-0.6
Mean Magnesium level (mg/dL)	Screening	2.1	2.1	2.1
	Colonoscopy Day	2.0	2.1	2.0
	Mean Change	-0.1	-0.1	-0.1
Mean Creatinine level (mg/dL)	Screening	0.9	0.9	0.9
	Colonoscopy Day	0.9	0.9	0.9
	Mean Change	0	0	0
Mean BUN level (mg/dL)	Screening	17.2	16.5	16.6
	Colonoscopy Day	12.1	12.4	12.7
	Mean Change	-5.1	-4.2	-4.0

Reference: Adapted from Study III Final Study Report, Table 12.4-1, Page 76

Table 32: Central tendencies of electrolyte measurements in the safety population in Study II

Laboratory Test	Measurement Day	Visicol 60 g[1] (n=30)	OsmoPrep 60 g[2] Split dose (3 pills) (n=32)	OsmoPrep 60 g[3] Split dose (4 pills) (n=29)	OsmoPrep 48 g[4] PM-only (n=30)	OsmoPrep 48 g[5] Split dose (n=33)	OsmoPrep 42 g[6] PM-only (n=33)	OsmoPrep 42 g[7] Split dose (n=31)
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mean Phosphate level (mg/dL)	Screening	3.4	3.5	3.3	3.4	3.4	3.5	3.5
	Colonoscopy Day	7.6	7.6	7.1	5.0	6.8	4.8	6.4
	Mean Change	4.2	4.1	3.8	1.6	3.4	1.4	2.8
Mean Sodium level (mEq/L)	Screening	141	141	141	141	141	141	141
	Colonoscopy Day	143	143	143	142	143	142	143
	Mean Change	2	2	2	1	2	2	1
Mean Potassium level (mEq/L)	Screening	4.3	4.3	4.2	4.2	4.3	4.2	4.2
	Colonoscopy Day	3.6	3.7	3.7	3.6	3.6	3.6	3.7
	Mean Change	-0.7	-0.7	-0.6	-0.6	-0.8	-0.6	-0.6
Mean Calcium level (mg/dL)	Screening	9.7	9.7	9.7	9.7	9.8	9.8	9.7
	Colonoscopy Day	9.2	9.2	9.3	9.0	9.1	9.3	9.2
	Mean Change	-0.5	-0.5	-0.4	-0.7	-0.7	-0.4	-0.5
Mean Magnesium level (mg/dL)	Screening	2.1	2.1	2.1	2.1	2.1	2.1	2.2
	Colonoscopy Day	2.0	2.1	2.1	2.1	2.0	2.0	2.1
	Mean Change	-0.1	-0.1	0	-0.1	-0.1	0	-0.1
Mean Creatinine level (mg/dL)	Screening	0.8	0.9	0.9	0.8	0.9	0.8	0.9
	Colonoscopy Day	0.9	0.9	0.9	0.9	0.9	0.8	0.9
	Mean Change	0	0	0	0	0	0	0
Mean BUN level (mg/dL)	Screening	17	17	16	16	17	16	18
	Colonoscopy Day	12	12	12	13	13	13	14
	Mean Change	-5	-5	-4	-3	-4	-4	-4

1 Visicol 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.

2 OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
3 OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 20 tablets.
4 OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 10 PM the evening before colonoscopy, 4 tablets every 15 minutes until 12 tablets.
5 OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 12 tablets.
6 OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 9 PM the evening before colonoscopy, 4 tablets every 15 minutes until 8 tablets.
7 OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 8 tablets.
Reference: Adapted from Study II Final Study Report, Table 12-4, Pages 63-64.

Medical Reviewer's Comments: The degree of hyperphosphatemia in all of the sodium phosphate treatment groups is consistent with historical sodium phosphate bowel preparation (including Visicol and OSPS) trials. The mean phosphate level more than doubled in all of the patients in Study III and in the Study II patients who received higher sodium phophate doses. The level of hyperphosphatemia was clearly proportional to the amount of sodium phosphate administration.

This medical officer believes that the level of hyperphosphatemia after OsmoPrep administration would be higher in patients with baseline hyperphosphatemia or baseline renal insufficiency.

The two evening-only OsmoPrep doses had lower mean phosphate levels then the other OsmoPrep dosing regimens who received the identical sodium phosphate dose. This medical officer believes that this is due to reporting error. The only post-treatment phosphate levels were performed on the day of the colonoscopy and no phosphate levels were performed on the evening prior to the colonoscopy dosing. This medical officer believes that phosphate levels performed after the second evening dose of the evening-only OsmoPrep regimens would result in higher mean phosphate levels.

The mean potassium and calcium levels significantly changed after sodium phosphate administration. The mean potassium change was about -0.7 mEq/L. Patients who have baseline hypokalemia (patients on diuretics) are in greater danger of having clinically significant hypokalemia after sodium phosphate administration.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Tables 33 and 34 display electrolyte abnormalities that occurred after patients received study treatment. Out of the 701 patients who had phosphorus blood tests on the day of colonoscopy (after receiving 60 grams of Visicol, 60 grams of OsmoPrep, or 48 grams of OsmoPrep), 666 (95%) of the patients developed high phosphate levels according to the sponsor's classification of normal phosphate levels.

Table 33: Electrolyte shifts from normal to abnormal in the safety population in Study III

Laboratory Abnormality	Visicol 60 g (n=238)* n/N (%)	OsmoPrep 60 g (n=236)* n/N (%)	OsmoPrep 48 g (n=239)* n/N (%)
Hyperphosphatemia	224/234 (96)	224/233 (96)	218/234 (93)
Hyponatremia	1/235 (<1)	0/235 (0)	0/236 (0)
Hypernatremia	15/235 (6)	39/235 (17)	22/236 (9)
Hypokalemia	46/230 (20)	50/228 (22)	41/227 (18)
Hypocalcemia	0/235 (0)	2/235 (<1)	5/236 (2)
Hypomagnesia	1/235 (<1)	0/235 (0)	1/236 (<1)

n = number of patients with the laboratory number
N = total number of patients who had the laboratory test
* The number of patients in the safety population in Study III. Not all of the patients had laboratory blood tests
Reference: Adapted from Study III Final Study Report, Table 10.2, Page 556

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Table 34: Electrolyte shifts from normal to abnormal in the safety population in Study II

Laboratory Abnormality	Visicol 60 g[1] (n=30)*	OsmoPrep 60 g[2] Split dose (3 pills) (n=32)*	OsmoPrep 60 g[3] Split dose (4 pills) (n=29)*	OsmoPrep 48 g[4] PM-only (n=30)*	OsmoPrep 48 g[5] Split dose (n=33)*	OsmoPrep 42 g[6] PM-only (n=33)*	OsmoPrep 42 g[7] Split dose (n=31)*
Parameter	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Hyperphosphatemia	27/28 (96)	30/31 (97)	27/27 (100)	10/28 (36)	31/32 (97)	8/33 (24)	24/29 (83)
Hyponatremia	0/27 (0)	0/30 (0)	0/29 (0)	0/27 (0)	0/31 (0)	0/33 (0)	0/29 (0)
Hypernatremia	3/27 (11)	2/30 (7)	5/29 (17)	1/27 (4)	6/31 (19)	1/33 (3)	3/29 (10)
Hypokalemia	8/27 (30)	5/30 (17)	4/26 (15)	2/26 (15)	5/30 (17)	6/33 (18)	5/28 (18)
Hypocalcemia	0/29 (0)	1/30 (3)	0/29 (0)	2/29 (7)	3/32 (9)	0/33 (0)	2/30 (7)
Hypomagnesia	0/29 (0)	0/31 (0)	0/29 (0)	0/28 (0)	0/32 (0)	0/33 (0)	0/30 (0)

1 Visicol 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
2 OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.
3 OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 20 tablets.
4 OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 10 PM the evening before colonoscopy, 4 tablets every 15 minutes until 12 tablets.
5 OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 12 tablets.
6 OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 9 PM the evening before colonoscopy, 4 tablets every 15 minutes until 8 tablets.
7 OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 8 tablets.
n = number of patients with the laboratory number
N = total number of patients who had the laboratory test
* The number of patients in the safety population in Study III. Not all of the patients had laboratory blood tests
Reference: Adapted from Study II Final Study Report, Table 10.3, Pages 248-253

Medical Reviewer's Comments: Almost every patient in Study III developed hyperphosphatemia. These results are consistent with prior Visicol and OSPS clinical trials.

Patients in Study III were not allowed to take their study drug unless they had baseline normal electrolytes including phosphate levels. This medical officer is concerned with the use of all

sodium phosphate bowel preparations including Visicol, OsmoPrep, and OSPS products in patients with baseline hyperphosphatemia.

Table 35 displays the sponsor's classification of the normal range of laboratory tests in Studies II and III.

Table 35: Classification the range of normal laboratory tests in Studies II and III

Test	Sex	Age	Normal Range
BUN	Both	18 - 80 years	4 - 24 mg/dL
Creatinine	Female	18 - 70 years	0.4 - 1.1 mg/dL
		70 - 80 years	0.4 - 1.4 mg/dL
		80 + years	0.4 - 1.4 mg/dL
	Male	18 - 50 years	0.5 - 1.2 mg/dL
		50 - 70 years	0.5 - 1.3 mg/dL
		70 - 80 years	0.5 - 1.5 mg/dL
		80 + years	0.5 - 1.6 mg/dL
Calcium	Both	18 + years	8.3 - 10.6 mg/dL
Phosphorus	Both	15 + years	2.2 - 5.1 mg/dL
Sodium	Both	18 - 59 years	132 - 147 mEq/L
		59 + years	135 - 145 mEq/L
Potassium	Both	18 + years	3.4 - 5.4 mEq/L
Bicarbonate	Both	18 - 70 years	17.0 - 30.6 mEq/L
		70 + years	17.0 - 32.0 mEq/L
Chloride	Both	18 + years	94 - 112mEq/L
Magnesium	Both	18 - 80 years	1.5 - 3.1 mg/dL
		80 + years	1.5 - 2.0 mg/dL

Reference: Study III, Section 16.5, Page 1667 and Study II, Section 16.5, Page 672.

Medical Reviewer's Comments: This medical officer believes that the sponsor's categorization of the range of "normal" laboratory ranges was too broad. Many laboratory centers classify a normal phosphorus range from 3.0 to 4.5 mg/dL, a normal calcium range from 9 to 10.5 mg/dL, a normal sodium range from 135 to 145 mEq/L, and a normal potassium range from 3.5 to 5.0 mEq/L. Therefore, if a patient receives a study drug (a sodium phosphate) and the patient's phosphorous increases to 5.0 mg/dL under the sponsor's classification, this patient did not develop hyperphosphatemia.

The sponsor's broad classification of normal electrolyte levels may underestimate the "real" frequencies of electrolyte abnormalities in the OsmoPrep trials.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Please see Section 7.1.7.3.2.

7.1.7.4 Additional analyses and explorations

Please see Section 7.1.7.3.2.

7.1.7.5 Special assessments

Studies II and III did not include liver tests (such as alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, and alkaline phosphatase), complete blood counts, or coagulation tests (such as INR and PTT).

Medical Reviewer's Comments: This medical officer believes that liver enzyme tests are less important for drug products for short-term use including OsmoPrep. Additionally, this medical officer is not aware of any sodium phosphate associated liver abnormality. However, this medical officer believes that routine liver testing should have been done because OsmoPrep is still an investigational new drug product.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Studies II and III, vital signs (including heart rate, blood pressure, respiratory rate, and temperature) were recorded at the Screening Visit and Visit 1 (the colonoscopy-day visit).

Medical Reviewer's Comments: This medical officer agrees with the sponsor's decision to incorporate symptomatic postural hypotension monitoring to evaluate dehydration in patients receiving a bowel preparation. However, this medical officer believes that the sponsor's classification of postural symptoms was too restricted. According to the sponsor, lightheadedness or dizziness symptoms (that occur in patients who are standing) must last 30 seconds to be classified as AEs. Although patients who develop orthostatic changes and symptoms that last for 20 seconds (while standing) are likely to be dehydrated, the sponsor would classify these events as AEs.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This medical officer selected Studies II and III to compare vital signs measurements in the treatment groups because these studies were the only two controlled studies submitted in this NDA, these studies contained the proposed patient population (patients who will undergo elective colonoscopy), and these studies included the proposed OsmoPrep dosing regimen. Furthermore, both Studies II and III had an active control treatment group (Visicol), an approved bowel preparation.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 36 displays the central tendencies of the vital sign measurements (supine and standing pulse) and weight assessments in Study III in which statistical differences in colonoscopy-day measurements compared to baseline measurements were present. However, the following vital signs in Study III did not demonstrate significant differences between the colonoscopy-day and baseline measurements: respiratory rate, supine and standing systolic blood pressure, and supine and standing diastolic blood pressure.

Table 36: Central tendencies of vital signs and weights in the safety population in Study III

Laboratory Test	Measurement Day	Visicol 60 g (n=235)	OsmoPrep 60 g (n=233)	OsmoPrep 48 g (n=236)
Supine Pulse (beats per minute)	Screening	69.1	68.6	68.8
	Colonoscopy Day	70.9	71.0	70.3
	Mean Change	2	2.3	1.5
Standing Pulse (beats per minute)	Screening	73.5	73.6	73.6
	Colonoscopy Day	77.1	77.6	75.3
	Mean Change	3.7	4.0	1.7
Weight (pounds)	Screening	179.4	180.9	181.1
	Colonoscopy Day	177.4	178.7	178.7
	Mean Change	-2.2	-2.2	-2.4

This table displays only vital signs and weights that demonstrated statistical significant differences in the colonoscopy-day and baseline measurements.
Reference: Adapted from Study III Final Study Report, Table 12.5-1, Page 80

Medical Reviewer's Comments: Patients who receive bowel preparations including sodium phosphate-based and PEG-based products commonly have decreased intravascular volume from decreased oral intake and diarrhea. These patients with intravascular depletion have lower stroke volume. In order to compensate for the lower stroke volume and maintain cardiac output, these patients have involuntarily increased heart rates. Therefore, the increased mean pulse rate in all three bowel preparations in Study III is a normal compensatory body response to intravascular depletion. This medical officer would expect most patients who receive bowel preparations have similar responses.

In Study III, the weight loss in all three treatment groups is consistent with patients who have diarrhea and decreased oral intake.

Patients who have baseline moderate to severe intravascular depletion should not receive OsmoPrep or other bowel preparations because these patients are likely to develop worsened intravascular volume depletion and possible complications.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There are no clinically significant vital sign outliers.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Please see Section 7.1.8.3.2

7.1.8.4 Additional analyses and explorations

In Studies II and III, patients were evaluated at the screening visit and Visit 1 for the presence of symptomatic postural hypotension, defined as the presence of orthostatic changes and postural symptoms. For the postural hypotension test, patients had their blood pressure and pulse measured in the supine position and then after three minutes of standing their vital signs were repeated and they were monitored for light-headedness, dizziness, and syncope.

Orthostatic changes were defined as an orthostatic pulse increase of 30 beets per minute or greater, accompanied by symptoms; an orthostatic decrease in systolic BP of 25 mmHg or greater, accompanied by symptoms; or an orthostatic decrease in diastolic BP of 10 mmHg or greater, accompanied by symptoms.

Postural symptoms (during the test of postural hypotension) included: lightheadedness lasting for at least 30 seconds; dizziness lasting for at least 30 seconds; or syncope of any duration. Episodes of symptomatic postural hypotension were classified as AEs; however, episodes of asymptomatic orthostatic hypotension were not categorized as AEs.

In Study III, 30 and 38 patients had baseline and colonoscopy-day orthostatic hypotension, respectively. Of the 38 patients in Study III who demonstrated orthostasis at the colonoscopy-day visit, 2 patients were classified with symptomatic postural hypotension. In Study II, 13 and 12 patients had baseline and colonoscopy-day orthostatic hypotension, respectively. In Study II, no patient had symptomatic orthostatic hypotension.

Medical Reviewer's Comments: This medical officer agrees with the sponsor's decision to incorporate symptomatic postural hypotension monitoring to evaluate dehydration in patients receiving a bowel preparation. However, this medical officer believes that the sponsor's classification of postural symptoms was too restricted. According to the sponsor, lightheadedness or dizziness symptoms (that occur in patients who are standing) had to last 30 seconds to have qualified as an AE. Although patients who develop orthostatic changes and symptoms that last for 20 seconds (while standing) are likely to be dehydrated, the sponsor would *not* classify these events as AEs.

In Study III, the Visicol and OsmoPrep 60 gram treatment groups had higher supine and standing heart rates at the colonoscopy-day visits compared to the OsmoPrep 48 gram treatment group. The higher the bowel preparation dose, the greater depletion of intravascular volume and the greater the compensatory increase in heart rate.

Since Studies II and III only had one post-treatment vital sign assessment (during the colonoscopy-day visit), a time dependency of vital sign abnormalities cannot be assessed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Studies II and III did not have any ECGs performed at baseline, during the treatment period, or after the treatment period.

Medical Reviewer's Comments: Electrolyte abnormalities (including hypokalemia and hypocalcemia) can increase a patient's risk of having an arrhythmia. Since sodium phosphate products have been associated with these electrolyte abnormalities and sodium phosphate products have been associated with post-marketing arrhythmias, this medical officer believes that clinical trials of new sodium phosphate products should have ECGs performed at baseline and frequently throughout the treatment period (including at C_{max}) to monitor for arrhythmias.

According to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,* "Evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new drug application."

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Studies II and III did not have any ECGs performed at baseline, during the treatment period, or after the treatment period. Not one OsmoPrep study included routine ECG monitoring.

Medical Reviewer's Comments: Please see my Medical Reviewer's Comments in Section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Studies II and III did not have any ECGs performed at baseline, during the treatment period, or after the treatment period. Not one OsmoPrep study included routine ECG monitoring.

Medical Reviewer's Comments: Please see my Medical Reviewer's Comments in Section 7.1.9.1.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Studies II and III did not have any ECGs performed at baseline, during the treatment period, or after the treatment period. Not one OsmoPrep study included routine ECG monitoring.

Medical Reviewer's Comments: Please see my Medical Reviewer's Comments in Section 7.1.9.1.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Studies II and III did not have any ECGs performed at baseline, during the treatment period, or after the treatment period. Not one OsmoPrep study included routine ECG monitoring.

Medical Reviewer's Comments: Please see my Medical Reviewer's Comments in Section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

Studies II and III did not have any ECGs performed at baseline, during the treatment period, or after the treatment period. Not one OsmoPrep study included routine ECG monitoring. In addition, the sponsor did not submit a thorough QT/QTc study in the NDA.

Medical Reviewer's Comments: According to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, "Drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization ("thorough QT/QTc study")."

Since the proposed OsmoPrep dose (48 grams) contains a lower dose of sodium phosphate than the approved Visicol dose (60 grams), this medical officer does not believe that the cardiac safety monitoring deficiencies preclude the approval of OsmoPrep. However, this medical officer recommends that the sponsor conduct a phase IV thorough QT/QTc study and labeling changes. Patients at high risk for cardiac arrhythmias (including patients with a history of ventricular arrhythmias, congestive heart failure, myocardial infarction, angina, and patients on concomitant medications that prolong the QT interval) should not take OsmoPrep.

7.1.10 Immunogenicity

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

7.1.11 Human Carcinogenicity

Since the proposed OsmoPrep dosage regimen is for short-term use — two days of treatment — human carcinogenicity studies were not required.

Non-clinical carcinogenicity studies were not required because of the proposed short duration of OsmoPrep use.

7.1.12 Special Safety Studies

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

7.1.13 Withdrawal Phenomena and/or Abuse Potential

According to the sponsor, all laxatives and purgatives (including OsmoPrep) have the potential for abuse by patients with eating disorders who "binge" and "purge".

The safety monitoring in Studies II and III was not adequate to detect withdrawal, abuse, or other post-dosing affects.

However, in clinical trials of other sodium phosphate products (such as Visicol), patients who received Visicol developed a reactive hypophosphatemia two-three days post-colonoscopy.

7.1.14 Human Reproduction and Pregnancy Data

There has been no exposure of pregnancy women to OsmoPrep.

7.1.15 Assessment of Effect on Growth

OsmoPrep was not studied in the pediatric population. Height measurements were not performed in the OsmoPrep development program.

7.1.16 Overdose Experience

According to the sponsor, there "have been no reported cases of overdosage with OsmoPrep. Purposeful or accidental ingestion of more than the recommended dosage of OsmoPrep might be expected to lead to severe electrolyte disturbances, including hyperphosphatemia, hypocalcemia, hypernatremia, or hypokalemia, as well as dehydration and hypovolemia, with attendant signs and symptoms of these disturbances. Certain severe electrolytes disturbances resulting from overdose may lead to cardiac ventricular arrhythmias, seizure, renal failure, and death. The patient who has taken an overdosage should be monitored carefully, and treated symptomatically for complications until stable."

7.1.17 Postmarketing Experience

OsmoPrep has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Of the 947 subjects/patients in the total safety population in this NDA (including the one phase 1 study, the one phase 2 trial, and the one phase 3 trial), 663 (70%) and 268 (28%) patients received OsmoPrep and Visicol, respectively. Of the 663 patients who received OsmoPrep in the safety population, 272 (41%) patients received the sponsor's proposed marketing OsmoPrep dosage regimen. Of the 268 patients who received Visicol in the safety population, 268 (100%) received the approved Visicol dosing regimen. Table 37 displays all of the studies submitted to NDA 21-892 (the OsmoPrep NDA). The table presents the study locations, designs, treatment groups, dosing schedules, and safety populations.

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Table 37: A Summary of all the studies submitted in this NDA

Study	Design	Treatment Groups	N*
Study I (102-04-02)	**Phase 1**, R, DB, SC, cross-over study to compare the purgative effect of PEG-8000 with an inactive vehicle in healthy male subjects **in the U.S.**	1) Period 1: PEG 8000 and inactive vehicle Period 2: Inactive vehicle 2) Period 1: Inactive vehicle Period 2: PEG 8000 and inactive vehicle	16
Study II (102-03-01)	**Phase 2**, R, investigator-blinded (open label to patient), MC study in adult patients scheduled for an elective colonoscopy **in the U.S.**	1) **Visicol** 60 grams (split doses – 30 grams in evening and 30 grams on day of colonoscopy) 2) **OsmoPrep** 60 grams (split doses – 30 grams over 1.5 hours in evening and 30 grams over 1.5 hours on day of colonoscopy) 3) **OsmoPrep** 60 grams (split doses – 30 grams over 1 hour in evening and 30 grams over 1 hour on day of colonoscopy) 4) **OsmoPrep** 48 grams (PM-only doses – 30 grams and then 18 grams in evening before colonoscopy) **5) OsmoPrep 48 grams (split doses – 30 grams in evening and 18 grams on day of colonoscopy)**** 6) **OsmoPrep** 42 grams (PM-only doses – 30 grams and then 12 grams in evening before colonoscopy) 7) **OsmoPrep** 42 grams (split doses – 30 grams in evening and 12 grams on day of colonoscopy)	30 32 29 30 **33** 33 31
Study III (102-04-01)	**Phase 3**, R, investigator-blinded (open label to patient), MC study in adult patients scheduled for an elective colonoscopy **in the U.S.**	1) **Visicol** 60 grams (split doses – 30 grams in evening and 30 grams on day of colonoscopy) 2) **OsmoPrep** 60 grams (split doses – 30 grams in evening and 30 grams on day of colonoscopy) **3) OsmoPrep 48 grams (split doses – 30 grams in evening and 18 grams on day of colonoscopy)****	238 236 **239**

* The safety population
** This OsmoPrep dosage regimen is the sponsor's proposed marketing OsmoPrep dosing regimen
R = randomized; DB = double-blind, SC = single center; MC = multicenter
Reference: Adapted from ISS, Table 1, Pages 14-16

Medical Reviewer's Comments: Of the 663 patients who received OsmoPrep in the safety population, 599 (90%) patients received an OsmoPrep dose that was equal or greater than the sponsor's proposed marketing OsmoPrep total dose.

This medical officer believes that the safety database exposure is acceptable. The OsmoPrep exposure (in number of patients who received equal to or greater than the proposed dose) represents the largest exposure to a bowel preparation product that was ever submitted to the FDA for approval. In addition, the duration of exposure (up to two days) is similar to the duration of exposure to other bowel preparations.

7.2.1.2 Demographics

Table 38 displays demographic characteristics in the OsmoPrep phase 2 and phase 3 studies (Studies II and III). Of the 931 patients in Studies II and III, 228 (24%) patients and 49 (5%) patients were ≥ 65 years old and ≥75 years, respectively.

Table 38: Demographic characteristics of the safety population in the OsmoPrep studies (Studies II and III)

		Visicol 60 g (split)[a]	OsmoPrep 60 g (split; 4 tablets)[b]	OsmoPrep 48 g (split)[c]	OsmoPrep 60 g (split; 3 tablets)[d]	OsmoPrep 48 g (PM)[e]	OsmoPrep 42 g (PM)[f]	OsmoPrep 42 g (split)[g]
Safety Population	N	268	265	272	32	30	33	31
Age	Mean age in years (SD)	57 (11)	55 (11)	56 (11)	56 (12)	56 (10)	53 (10)	61 (13)
	≥ 65 years old (%)	77 (29)	57 (22)	63 (23)	9 (28)	5 (17)	4 (12)	13 (42)
	≥ 75 years old (%)	16 (6)	10 (4)	15 (6)	1 (3)	1 (3)	0 (0)	6 (19)
Gender	Male N (%)	116 (43)	124 (47)	120 (44)	17 (53)	13 (43)	14 (42)	13 (42)
	Female N (%)	152 (57)	141 (53)	152 (56)	15 (47)	17 (57)	19 (58)	18 (58)
Race	Caucasian, N (%)	228 (85)	236 (89)	242 (89)	32 (100)	24 (80)	30 (91)	25 (81)
	Black, N (%)	33 (12)	21 (8)	26 (10)	0 (0)	5 (17)	3 (9)	4 (13)
	Hispanic, N (%)	14 (5)	16 (6)	13 (5)	0 (0)	1 (3)	1 (3)	1 (3)
	Asian, N (%)	2 (1)	3 (1)	2 (1)	0 (0)	1 (3)	0 (0)	1 (3)
	Other, N (%)	5 (2)	5 (2)	2 (1)	0 (0)	0 (0)	0 (0)	1 (3)
Height in inches	Mean (SD)	67 (4)	67 (4)	67 (4)	68 (4)	67 (4)	67 (3)	66 (4)
Weight in pounds	Mean (SD)	181 (37)	184 (43)	182 (40)	184 (42)	191 (38)	185 (37)	183 (48)

a Visicol 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets (40 total tablets).
b OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 20 tablets (40 total tablets).
c OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 12 tablets (32 total tablets).
d OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets (40 total tablets).
e OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 10 PM the evening before colonoscopy, 4 tablets every 15 minutes until 12 tablets (32 total tablets).
f OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 9 PM the evening before colonoscopy, 4 tablets every 15 minutes until 8 tablets (28 total tablets).
g OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 8 tablets (28 total tablets).
Reference: ISS, Section 2.2.2, Table 6, Pages 31-32

Medical Reviewer's Comments: Overall, the baseline demographics of the study populations in Studies II and III were acceptable. The mean age was similar amongst the treatments groups in Studies II and III. In Study III, the mean age was about 56.

The racial diversity in the two studies was similar to the racial diversity in the United States; except the study populations had a lower percentage of Hispanics and a higher percentage of Caucasians.

7.2.1.3 Extent of exposure (dose/duration)

Table 39 presents the extent of exposure to OsmoPrep and Visicol in the safety population. Patients scheduled for a colonoscopy received their entire dose, within 24 hours before their colonoscopy with their first dose in the evening before the colonoscopy.

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Table 39: Exposure to OsmoPrep and Visicol in the safety population

Exposure[a]	Visicol[b] 60 g (N=268)	INKP-102									
		All patients (N=663)	60 g			48 g			42 g		
			3 tabs split[c] (N=32)	4 tabs split[d] (N=265)	Total (N=297)	4 tabs evening[e] (N=30)	4 tabs split[f] (N=272)	Total (N=302)	4 tabs evening[g] (N=33)	4 tabs split[h] (N=31)	Total (N=64)
Dose, g											
N	268	663	32	265	297	30	272	302	33	31	64
Mean	59.1	52.2	60	59.1	59.2	48	47.5	47.6	41.6	41.4	41.5
Median	60	48	60	60	60	48	48	48	42	42	42
SD	4.62	7.56	0	4.48	4.24	0	3.89	3.7	2.09	2.38	2.22
Range	27, 60	2, 60	60, 60	30, 60	30, 60	48, 48	2, 50	2, 50	30, 42	30, 42	30, 42
Treatment compliance (%)											
N	268	663	32	265	297	30	272	302	33	31	64
Mean	98.5	98.9	100	98.5	98.6	100	99.1	99.2	99.1	98.6	98.9
Median	100	100	100	100	100	100	100	100	100	100	100
sd	7.68	7.2	0	7.42	7.02	0	8.13	7.72	5.05	5.71	5.34
Range	45, 100	3, 106	100, 100	50, 100	50, 100	100, 100	3, 106	3, 106	71, 100	71, 100	71, 100
≤70	6 (2)	8 (1)	0	6 (2)	6 (2)	0	2 (<1)	2 (<1)	0	0	0
>70% to 80%	1 (<1)	4 (<1)	0	2 (<1)	2 (<1)	0	0	0	1 (3)	1 (3)	2 (3)
>80% to 90%	4 (1)	14 (2)	0	7 (3)	7 (2)	0	6 (2)	6 (2)	0	1 (3)	1 (2)
>90% to 95%	2 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0	0	0	0	0	0
>95% to 99%	4 (1)	1 (<1)	0	1 (<1)	1 (<1)	0	0	0	0	0	0
100%	251 (94)	635 (96)	32 (100)	248 (94)	280 (94)	30 (100)	264 (97)	294 (97)	32 (97)	29 (94)	61 (95)

SD = Standard deviation

a Patients were to take study drug within 24 hours before colonoscopy

b Visicol 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.

c OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 3 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 3 tablets every 15 minutes until 20 tablets.

d OsmoPrep 60 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 20 tablets.

e OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 10 PM the evening before colonoscopy, 4 tablets every 15 minutes until 12 tablets.

f OsmoPrep 48 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 12 tablets.

g OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then at 9 PM the evening before colonoscopy, 4 tablets every 15 minutes until 8 tablets.

h OsmoPrep 42 grams of sodium phosphate: beginning at 6 PM the evening before colonoscopy, 4 tablets every 15 minutes until 20 tablets, then in the AM on the day of colonoscopy, 4 tablets every 15 minutes until 8 tablets.

Reference: ISS, Table 3, Page 25

Medical Reviewer's Comments: See Section 7.2.3 for the Medical Reviewer's Comments.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

This OsmoPrep NDA does not contain any secondary clinical data sources used to evaluate safety.

7.2.2.2 Postmarketing experience

OsmoPrep has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2.2.3 Literature

OsmoPrep is a new sodium phosphate formulation and has not been studied in the literature.

7.2.3 Adequacy of Overall Clinical Experience

Medical Reviewer's Comments: Of the 663 patients who received OsmoPrep in the safety population, 599 (90%) patients received an OsmoPrep dose that was equal or greater than the sponsor's proposed marketing OsmoPrep total dose (48 grams of sodium phosphate).

This medical officer believes that the OsmoPrep safety database is acceptable. The OsmoPrep exposure (the number of patients who received ≥ than the proposed OsmoPrep dose) represents the largest exposure to a bowel preparation product (including the GoLYTELY, NuLYTELY, HalfLytely, and Visicol safety databases) that was ever submitted to the FDA for approval. In addition, the duration of exposure (over 13 hours of exposure) is similar to the duration of exposure to other bowel preparations.

This medical officer believes that the design of the two OsmoPrep trials (randomized, investigator-controlled, active controlled, and multi-center) is consistent with prior bowel preparation designs and was adequate to answer critical questions.

However, this medical officer believes that the groups that were excluded from participation in the OsmoPrep trials (including patients with serum creatinine >1.4 mg/dL, known or suspected abnormalities in serum electrolytes, ascites, and untreated dysrhythmias) limit the relevance of the OsmoPrep safety evaluation. In addition, patients who had asymptomatic electrolyte abnormalities (including sodium, potassium, calcium, phosphate, and magnesium abnormal levels) were not allowed to start study treatment and were dropped from the study. Since the OsmoPrep studies excluded these populations, healthcare providers should be warned about the lack of safety assessments in these populations. This medical officer recommends that all of the above populations should be listed in the WARNINGS section (if they are not listed in the CONTRAINDICATIONS section) of the label.

Additionally, a thorough QT/QTc study was not performed in a product that is known to cause electrolyte abnormalities. Therefore, this medical officer recommends a phase IV commitment for a thorough QT/QTc study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

According to Dr. Tamal Chakraborti (the pharmacology/toxicology reviewer), NDA 21-892 for OsmoPrep ... provided adequate assurance of safety for its proposed oral use." "From a

preclinical standpoint, this 505(b)(2) application contains adequate information, meets the guidelines and satisfies the criteria for marketing authorization of OsmoPrep."

7.2.5 Adequacy of Routine Clinical Testing

Medical Reviewer's Comments: This medical officer believes that the vital sign testing including the orthostatic measurements were adequate for a bowel preparation product.

This medical officer believes that the frequency of routine clinical laboratory testing (including sodium, potassium, creatinine, BUN, phosphate, and calcium blood tests) was suboptimal. Since sodium phosphate products have been associated with serious post-marketing electrolyte abnormalities including acute phosphate nephropathy and some of these events presented weeks after the colonoscopy, this medical officer believes that the two OsmoPrep trials should have had follow-up safety laboratory testing (at least one week after colonoscopy).

Additionally, the two OsmoPrep studies did not have adequate ECG testing — no baseline ECG or treatment period ECGs were performed. According to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,* "Evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new drug application." Thus, all products should have routine ECG testing during phase 2 and phase 3 testing, especially products that have been associated with hypocalcemia and hypokalemia.

Electrolyte abnormalities (including hypokalemia and hypocalcemia) can increase a patient's risk of having an arrhythmia. Since sodium phosphate products have been associated with these electrolyte abnormalities and sodium phosphate products have been associated with post-marketing arrhythmias, this medical officer believes that clinical trials of new sodium phosphate products should have ECGs performed at baseline and frequently throughout the treatment period (including at C_{max}) to monitor for arrhythmias.

Furthermore, routine coagulation laboratory testing (INR, PTT, and platelet counts) were not performed at baseline or during the treatment period. Routine CBCs were not performed at baseline or during the treatment period.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

According to Dr. Suliman Al-Fayoumi, the biopharmaceutics reviewer, sodium and phosphate ions are unlikely to be associated with any significant drug-drug interaction. Please see his review for further details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Medical Reviewer's Comments: A thorough QT/QTc study was not performed in this NDA. According to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,* "Drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization ("thorough QT/QTc study")."

Since the proposed OsmoPrep dose (48 grams) contains a lower dose of sodium phosphate than the approved Visicol dose (60 grams), this medical officer does not believe that the cardiac safety monitoring deficiencies preclude the approval of OsmoPrep. However, this medical officer recommends that the sponsor conduct a phase IV thorough QT/QTc study. Also, this medical officer recommends that the WARNINGS section of the OsmoPrep label should include warnings about OsmoPrep use in patients at high risk for cardiac arrhythmias (including patients with a history of ventricular arrhythmias, congestive heart failure, myocardial infarction, angina, and patients on concomitant medications that prolong the QT interval).

7.2.8 Assessment of Quality and Completeness of Data

The overall quality and completeness of the data was acceptable.

7.2.9 Additional Submissions, Including Safety Update

The OsmoPrep Safety Update, submitted on February 22, 2006, included the following:

- Information from their ongoing phase 3 study (INKP-102-05-01) entitled, "*MCC-free Sodium Phosphate Tablets versus Marketed HalfLytely® with Bisacodyl Tablets Bowel Prep Kit for Colon Cleansing: An Investigator-blinded, Randomized, Multi-center Trial (SPARKLE).*" This U.S. study is an ongoing, multicenter (10 sites), randomized, investigator blinded comparison of 48 grams of OsmoPrep (the proposed dosing regimen in this NDA) with the marketed HalfLytely® with Bisacodyl Tablets Bowel Prep Kit in adults undergoing a scheduled colonoscopy. In this study, enrollment was closed and of the 481 randomized patients, 411 have completed their colonoscopy. As of February 17, 2006, there have been no deaths or drug-related SAEs. There has been one reported case of drug-related study treatment discontinuation. A 22 year old female developed nausea, vomiting, and bloating after taking the colon preparation and withdrew from the study before she had the colonoscopy. Her study treatment remains blinded.
- Four publications describing case reports of renal failure and acute phosphate nephropathy.

Medical Reviewer's Comments: The sponsor's Safety Update does not change this medical officer's conclusions regarding the safety of OsmoPrep. This medical officer proposed labeling changes includes renal failure and acute phosphate nephropathy in the WARNINGS section of the OsmoPrep label.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Please see Section 1.3.3 (Safety Summary of Clinical Finding in the Executive Summary) for a summary of important drug-related AEs, important limitations of the data, and safety conclusions.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Since this NDA involved only two studies (Studies II and III), no pooling of safety (or efficacy) data was performed in this NDA review.

7.4.1.2 Combining data

Since this NDA involved only two studies (Studies II and III), no pooling of safety (or efficacy) data was performed in this NDA review.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The most common AEs and drug-related AEs appear to be related to the sodium phosphate dose. The higher the sodium phosphate dose the higher the frequency of GI AEs and drug-related GI AEs including abdominal distension, nausea, abdominal pain, and vomiting. Similarly the greater the sodium phosphate dose, the greater the mean change in phosphate level.

The OsmoPrep 60 gram and the Visicol 60 gram treatment groups had a similar frequency of common AEs and drug-related common AEs in Study III. The OsmoPrep 48 gram treatment group had a lower frequency of these AEs compared to the 60 gram sodium phosphate groups. Thus, the dose of sodium phosphate used in Study III correlated more with the frequency of AEs than the product formulation.

7.4.2.2 Explorations for time dependency for adverse findings

Since the two OsmoPrep studies were of short duration (the blinded treatment period was less than 24 hours), and the full AE assessments were only taken once (at Visit 1 before the colonoscopy), an assessment of time-dependency of adverse findings is not possible.

7.4.2.3 Explorations for drug-demographic interactions

Please see Section 8.3 for explorations of drug-demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

There were no clear drug-disease interactions. However, the two OsmoPrep trials excluded patients with significant concomitant medical illness including patients with renal insufficiency; known or suspected abnormalities in serum electrolytes or blood count; gastrointestinal, heart or liver disease of any kind; ascites or untreated dysrhythmias; recent history of acute gastroenteritis; recent history of laxative use (including fiber supplements); and any other clinically significant disease or finding that, in the opinion of the investigator, would expose the subject to an increased risk of a significant AE. Since the OsmoPrep studies contained a limited population, it is not possible to predict drug-disease interactions on the excluded populations.

7.4.2.5 Explorations for drug-drug interactions

There were no clear drug-drug interactions in this NDA.

7.4.3 Causality Determination

Please see Section 7.3 (Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions) for information about causality.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Of the two OsmoPrep doses in the phase 3 trial (Study III), the sponsor only proposes to market the 48 gram sodium phosphate dose. The sponsor's proposed dosing regimen comprises of 32 OsmoPrep tablets containing 48 grams of sodium phosphate taken with a total of 2 quarts of clear liquid with the following instructions:

> The night before colonoscopy: Starting at 6:00 PM, patients should take 4 tablets at a time with 8 ounces of clear liquid every 15 minutes (over 1 hour) for a total of 20 tablets containing 30 grams of sodium phosphate.
> The day of the colonoscopy: Starting 3 to 5 hours prior to the colonoscopy, patients should take 4 tablets at a time with 8 ounces of clear liquid every 15 minutes (over 0.5 hours) for a total of 12 tablets containing 18 grams of sodium phosphate.

Medical Reviewer's Comments: This medical officer agrees with the sponsor's dose and dosage regimen selection for adults. The OsmoPrep 48 gram dose (compared to Visicol) was as efficacious as the higher OsmoPrep dose — 60 grams — (compared to Visicol). Furthermore, the OsmoPrep 48 gram dose had lower frequencies of GI AEs and GI drug-related AEs (including abdominal distension, nausea, abdominal pain, and vomiting) and had lower changes in the mean phosphate levels.

8.2 Drug-Drug Interactions

The OsmoPrep trials did not have any unequivocal drug-drug interactions.

8.3 Special Populations

Gender — Efficacy: There were no appreciable differences in the proportion of patients who responded to the Overall Colon Cleansing Scale based upon gender. In Study III, the Overall Colon Cleansing response rate (primary efficacy assessment) was **96%** and 95%, respectively for **men** and women taking 48 g of OsmoPrep; **98%** and 96%, respectively, for **men** and women taking 60 g of OsmoPrep; and **91%** and 97%, respectively, for **men** and women taking the Visicol comparator. In addition, men and women had similar results in the important secondary efficacy endpoints.

Gender — Safety: Overall, there were no appreciable differences in the proportion of patients who had AEs based upon gender. By far the most common AEs in men and women were GI disorders (including abdominal distension, abdominal pain, nausea, and vomiting). A higher percentage of women in all three treatment groups had nausea and vomiting compared to the percentage of men who experienced nausea or vomiting. In Study III, 54 (40%), 58 (45%), and 50 (37%) women in the Visicol, OsmoPrep 60 grams, and OsmoPrep 48 grams treatment groups experienced nausea. In Study III, 21 (20%), 35 (33%), and 16 (15%) men in the Visicol, OsmoPrep 60 grams, and OsmoPrep 48 grams treatment groups experienced nausea. In Study III, 14 (10%), 14 (11%), and 10 (7%) women in the Visicol, OsmoPrep 60 grams, and OsmoPrep 48 grams treatment groups vomited. In Study III, 4 (4%), 8 (7%), and 0 (0%) men in the Visicol, OsmoPrep 60 grams, and OsmoPrep 48 grams treatment groups vomited. For both men and women, the patients who received higher sodium phosphate doses (60 grams) experienced more GI AEs.

Race — Efficacy: In the All Assessed Population in Study III, there were 615, 73, 6, and 10 Caucasians, Blacks, Asians, and Other Racial Groups, respectively. The 41 patients of Hispanic descent were included the racial subgroups. There were no appreciable differences in the proportion of patients who responded to Overall Colon Cleansing based upon race or ethnicity. In the phase 3 study, the overall colon cleansing response rate (primary efficacy assessment) was 96% each for Caucasians and Blacks taking 48 grams of OsmoPrep; 98% and 94%, respectively, for Caucasians and Blacks taking 60 grams of OsmoPrep; and 94% and 93%, respectively, for Caucasians and Blacks taking the Visicol comparator. Since Study III had insufficient number of Asian patients (only six Asian patients), efficacy differences between Asians and other racial populations were not performed.

Race — Safety: The most common AEs experienced in each racial group were GI disorders (including abdominal distention, nausea, abdominal pain, and vomiting). Headache, dizziness, and orthostatic hypotension were also experienced by more than 1% of patients in at least 1 racial group. There were no appreciable differences in the proportion of Caucasian and Black patients who experienced a GI AE. Since there were insufficient numbers of Asian, Other Racial Groups, and Hispanics in Studies II and III, safety differences between these racial populations were not performed.

Geriatrics — Efficacy: Out of the 918 patients in the AAP population in Studies II and III, 225 (25%) patients were ≥ 65 years old. There were no appreciable differences in the proportion of patients who responded to overall colon cleansing (primary efficacy assessment) based upon age group. In the phase 3 study, the overall colon cleansing response rate (primary efficacy assessment) was 94% and **100%**, respectively for patients less than 65 and **geriatric patients** taking 48 grams of OsmoPrep; 96% and **100%**, respectively for patients less than 65 and **geriatric patients** taking 60 grams of OsmoPrep; and 93% and **97%**, respectively for patients less than 65 and **geriatric patients** taking the Visicol comparator. Of the 225 geriatric patients in the AAP population in Studies II and III in all OsmoPrep and Visicol groups, 220 (98%) geriatric patients were considered responders to the primary efficacy assessment.

Out of the 918 patients in AAP population in Studies II and III, 47 (5%) patients were ≥ 75 years old. For the overall colon cleansing (primary efficacy) assessment, all 47 patients who were ≥ 75 years in Studies II and III were responders. Thus, 100% of the patients who were ≥ 75 years old responded to OsmoPrep 48 grams, OsmoPrep 60 grams, and the Visicol comparator.

Geriatrics — Safety: The most common AEs experienced in each age group were GI disorders (including abdominal distention, nausea, abdominal pain, and vomiting). There were no appreciable differences in the proportion of geriatric patients and patients less than 65 years old who experienced AEs. Additionally, patients greater than 75 years old did not have higher frequencies of GI AEs compared to patients less than 65 years old and patients between 65 and 74 years old.

Medical Reviewer's Comments: A laboratory abnormality, including a severe laboratory abnormality, was not classified in the OsmoPrep trials as an AE, unless the laboratory abnormality was associated with an AE. In a sodium phosphate bowel preparation trial in 70 patients who were to have elective colonoscopy, older patients had higher phosphate levels compared to younger patients (Gumurdulu 2004). In this trial, patients between the ages of 25-35, 36-45, 46-55, and over 56 years old (who received oral sodium phosphate solution) had post-treatment phosphate levels of 6.8, 6.8, 7.7, and 9.0 mg/dL, respectively.

Similarly, in Study III older patients had higher post-treatment phosphate levels in all three treatment groups (see Table 40). In all three sodium phosphate treatment groups, the mean phosphate levels in patients 18-64, 65-74, and ≥ 75 years old in Study III were 7.4, 7.9, and 8.0 mg/dL, respectively. The mean phosphate levels in patients 18-64, 65-74, and ≥ 75 years old who received 48 grams of OsmoPrep (the proposed marketing dose) in Study III were 7.0, 7.3, and 8.0 mg/dL, respectively.

Table 40: Mean phosphate measurements (in mg/dL) according to age in the safety population in Study III

Age range in years	Measurement Day	Visicol 60 g (n=235) n (%)	OsmoPrep 60 g (n=233) n (%)	OsmoPrep 48 g (n=236) n (%)	All Patients (n=713) n (%)
18-64 (n=536)	Screening	3.6	3.5	3.6	3.6
	Colonoscopy Day	7.4	7.8	7.0	7.4
	Mean Change	3.8	4.3	3.4	3.8
65-74 (n=143)	Screening	3.5	3.5	3.5	3.5
	Colonoscopy Day	8.2	8.2	7.3	7.9
	Mean Change	4.7	4.7	3.8	4.4
≥ 75 (n=34)	Screening	3.1	3.8	3.6	3.5
	Colonoscopy Day	7.5	8.5	8.0	8.0
	Mean Change	4.5	4.7	4.4	4.5

Reference: Adapted from Study III Study Report, Table 10.1.1h (Page 490), Table 10.1.1i (Page 499), and Table 10.1.1j (Page 508)

Table 41 displays the mean potassium measurements in mEq/L according to three age ranges in the safety population in Study III. In Study III, the mean change in potassium levels in patients 18-64, 65-74, and ≥ 75 years old were -0.6, -0.7, and -0.8 mEq/L, respectively. The mean changes in potassium levels in patients 18-64, 65-74, and ≥ 75 years old who received 48 grams of OsmoPrep (the proposed marketing dose) in Study III were -0.6, -0.7, and -0.9 mEq/L, respectively.

Table 41: Mean potassium measurements (in mEq/L) according to age in the safety population in Study III

Age range in years	Measurement Day	Visicol 60 g (n=235) n (%)	OsmoPrep 60 g (n=233) n (%)	OsmoPrep 48 g (n=236) n (%)	All Patients (n=713) n (%)
18-64 (n=536)	Screening	4.3	4.3	4.3	4.3
	Colonoscopy Day	3.7	3.7	3.7	3.7
	Mean Change	-0.7	-0.6	-0.6	-0.6
65-74 (n=143)	Screening	4.4	4.3	4.4	4.4
	Colonoscopy Day	3.6	3.7	3.7	3.7
	Mean Change	-0.8	-0.6	-0.7	-0.7
≥ 75 (n=34)	Screening	4.4	4.8	4.5	4.6
	Colonoscopy Day	3.8	3.6	3.7	3.7
	Mean Change	-0.6	-1.0	-0.9	-0.8

Reference: Adapted from Study III Study Report, Table 10.1.1h (Page 487), Table 10.1.1i (Page 496), and Table 10.1.1j (Page 505)

Medical Reviewer's Comments: There appears to be a positive correlation between increasing age and increased phosphate blood levels after sodium phosphate administration.

Hepatic Insufficiency: Patients with known liver disease and patients with ascites were excluded from the two OsmoPrep studies. Additionally, liver enzyme tests and liver function tests (INR and albumin) were not measured at screening or post study treatment.

According to the **Hepatic insufficiency** subdivision of the **Special Populations** section of the **CLINICAL PHARMACOLOGY** section of the Visicol label, "The ionized, inorganic form of phosphate in the circulating plasma is excreted by the kidneys. Visicol is not expected to be metabolized in the liver." Since OsmoPrep contains the identical active ingredient as Visicol (sodium phosphate), OsmoPrep is likely to have the identical effect in hepatic insufficiency patients.

Medical Reviewer's Comments: Thus, there will be no special dosing considerations in patients with hepatic insufficiency. However, since patients with severe hepatic insufficiency are likely to have electrolyte abnormalities, this medical officer recommends pre-dose and post-dose laboratory testing (including electrolytes, creatinine, BUN, phosphate, calcium, and magnesium levels).

Renal Insufficiency: Patients with a creatinine > 1.4 mg/dL were excluded from the OsmoPrep clinical trials. According to the **Renal insufficiency** subdivision of the **Special Populations** section of the **CLINICAL PHARMACOLOGY** section of the Visicol label, "Since the ionized, inorganic form of phosphate in the circulating plasma is excreted almost entirely by the kidneys, patients with renal disease may have difficulty excreting a large phosphate load." Since OsmoPrep has the identical active ingredient (sodium phosphate) as Visicol, this statement applies to OsmoPrep. Additionally, there have been post-marketing reports of acute phosphate nephropathy and acute renal failure in patients who took sodium phosphate products.

Medical Reviewer's Comments: Thus, this medical officer recommends that patients with renal disease have pre-dosing and post-dosing laboratory tests (including electrolytes, calcium, phosphate, creatinine, and BUN) after OsmoPrep administration.

Pregnancy: All pregnant patients were excluded from the OsmoPrep trials and no patient in the trials became pregnant. According to the **Pregnancy** subsection of the **PRECAUTIONS** section of the Visicol label, "Reproduction studies have not been conducted with Visicol. It is also not known whether Visicol can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Visicol Tablets should be given to a pregnant woman only if clearly needed."

Since OsmoPrep was not studied in pregnant patients, OsmoPrep should not be used in pregnant woman unless clearly needed.

8.4 Pediatrics

All of the OsmoPrep studies have excluded subjects/patients less than 18 years old and no pediatric patient has received OsmoPrep in the OsmoPrep studies.

Pediatric Regulatory Summary: The following is a summary of the major pediatric regulatory events regarding sodium phosphate products in the DGP:

- On September 6, 2000, Dr. Steven Aurecchia, the deputy division director of the Division of Gastrointestinal and Coagulation Drug Products (the FDA division which became the DGP) at the time of the Visicol approval, wrote the following in his Division Director review of Visicol, "A pediatric waiver has been granted. Visicol would not be used in a substantial number of pediatric patients, as colonoscopy is not frequently performed in this population. In addition, NuLYTELY is labeled for use down to 6 months of age, and may be more appropriate as a liquid formulation." Therefore, Visicol was given a waiver for pediatric studies.
- In the August 2004 end of phase 2 meeting between the sponsor and the DGP, the sponsor had the following comments and question for the DGP: "We believe that the factors that justified the waiver for Visicol also justify a waiver for INKP-102 (OsmoPrep). Does FDA agree that InKine does not need to provide pediatric data for INKP-102 (OsmoPrep)?" In the meeting, the DGP responded with the following statement: "A waiver for pediatric studies may be acceptable; however, you should submit a formal request."

Sponsor's Pediatric Full Waiver Justification: In this NDA, the sponsor of OsmoPrep requests a full waiver of its obligation to provide data regarding the use of OsmoPrep in pediatric patients pursuant to 21 CFR 314.55(c)(2)(i) and 314.55(c)(2)(iii).

The sponsor argues that according to 21 CFR 314.55(c)(2)(i), a full waiver can be granted if "The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients." The sponsor states that "there are no data to indicate that OsmoPrep would be more effective or more safe, with regard to treatment limiting AEs, than available agents in pediatric patients." Also the sponsor states that OsmoPrep "is likely to be associated with poorer compliance in pediatric patients than the currently available liquid purgative products." "Most children would be unable, or at best very reluctant, to swallow the number of large tablets necessary for adequate purgation."

The sponsor argues that according to 21 CFR 314.55(c)(2)(iii) a full waiver can be granted if there "is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups." According to the sponsor, IBD pediatric patients would be at higher risk of "excessive absorption of sodium and phosphate" from OsmoPrep administration. In addition, young "pediatric patients" might be at risk for symptomatic hypovolemia" and "NuLYTELY (an approved pediatric colon preparation) is believed not to cause osmotic shifts of fluid and would thus be a more appropriate purgative for pediatric patients."

Medical Reviewer's Comments: This medical officer believes that our division should grant a full waiver to the sponsor of OsmoPrep to conduct pediatric studies. Currently, NuLYTELY is approved for "bowel cleansing prior to colonoscopy" in pediatric patients ≥ six months of age. Furthermore, OSPS is professionally labeled OTC for colon cleansing in pediatric patients ≥ 12 years of age. Therefore, multiple colon preparations are available for pediatric patients ≥ 12 months of age and one colon preparation is available for pediatric patients ≥ six

months of age. Sodium phosphate products (OSPS, Visicol, and OsmoPrep) containing identical amounts of sodium phosphate are likely to be equally efficacious and safe in pediatric patients. Therefore, OsmoPrep is not likely to "represent a meaningful therapeutic benefit over existing treatments for pediatric patients". In addition, colon preparation is not performed in a substantial number of pediatric patients. Thus, this medical officer recommends a full pediatric waiver for the study of OsmoPrep in pediatric patients.

8.5 Advisory Committee Meeting

There were no Advisory Committee Meetings related to OsmoPrep.

8.6 Literature Review

Please see Section 11 (References) for a list of the references used in this review.

8.7 Postmarketing Risk Management Plan

This medical officer does not recommend a post-marketing risk management plan.

8.8 Other Relevant Materials

There are no additional relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor's proposed 48 gram OsmoPrep dosing regimen demonstrated efficacy in two well-controlled clinical studies of patients who received an elective colonoscopy.

Given the known post-marketing serious electrolyte abnormalities associated with serious AEs (including renal failure, acute phosphate nephropathy, seizures, and ventricular arrhythmias) after sodium phosphate administration, the following are the major deficiencies in the OsmoPrep safety monitoring in Studies II and III:

1) Lack of any post-colonoscopy blood tests;
2) Lack of any post-colonoscopy follow-up safety visits;
3) Lack of any screening, treatment period, or post-treatment period ECGs performed;
4) No thorough QT/QTc study performed; and
5) Lack of information on the safety and efficacy of OsmoPrep in renal insufficiency patients.

Since the OsmoPrep clinical studies excluded a wide range of patient disorders (renal insufficiency; known or suspected electrolyte disorders; untreated dysrhythmias; gastrointestinal, heart, or liver

disease of any kind; ascites; recent acute gastroenteritis; recent laxative use; and/or recent constipation), extrapolation of the OsmoPrep safety database to other populations is limited.

This medical officer believes that the sponsor's safety database exposure was acceptable. In addition, the sponsor's proposed 48 gram OsmoPrep dosing regimen appears to have an improved safety profile compared with the approved and marketed 60 gram Visicol regimen and the 48 gram OsmoPrep dosing regimen contains a lower dose of sodium phosphate; therefore, this medical officer believes that the OsmoPrep safety program will be adequate for approval if the following two conditions are met by the sponsor:

1) Labeling changes are made to reflect the above deficiencies in the OsmoPrep safety program; and
2) A commitment is made to perform a phase 4 post-marketing commitments to conduct a thorough QT/QTc study in healthy subjects and a pharmacokinetic study in renal insufficiency patients.

This medical officer agrees with the sponsor's proposed 48 gram OsmoPrep dose regimen (with a total of 2 quarts of clear fluid) for adults for colon preparation before a colonoscopy.

9.2 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends **approval** of the 48 gram OsmoPrep™ (sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP) dose regimen for cleansing of the large bowel as a preparation for colonoscopy in adults ≥ 18 years of age if the sponsor agrees to important labeling changes and agrees to two phase IV commitments. If the sponsor does not agree to the important labeling changes and to the two phase IV commitments, then this medical officer recommends an **approvable** action.

This medical officer recommends adding **WARNINGS** to the OsmoPrep label about the risk of SAEs and electrolyte changes after OsmoPrep administration in patients with the following risk factors: renal insufficiency, history of acute phosphate nephropathy, electrolyte disorders, seizures, and patients at increased risk of ventricular arrhythmias. Additionally, this medical officer recommends phase 4 commitments to conduct a thorough QT/QTc study of OsmoPrep in healthy subjects and a pharmacokinetic study in patients with renal insufficiency.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk Management Activities are not indicated.

9.3.2 Required Phase 4 Commitments

This medical officer recommends one phase 4 post-marketing commitment to conduct a thorough QT/QTc study of OsmoPrep in healthy subjects because the sponsor did not submit a thorough QT/QTc study in this NDA, did not submit a thorough QT/QTc study for Visicol (under NDA 21-

5) The **CONTRAINDICATIONS** section should not include diseases (including [redacted]) that are unknown hazards. The **WARNINGS** section of the label should include these diseases;
6) The **WARNINGS** section should include specific information about patients with renal insufficiency, electrolyte disorders, a history of acute phosphate nephropathy, seizures, and arrhythmias;
7) The **PRECAUTIONS** section should recommend that pre-dose and post-colonoscopy ECGs should be performed in patients with a known prolonged QT;
8) The **Geriatric Use** subsection of the **PRECAUTIONS** section should include the frequencies of hyperphosphatemia of geriatric patients in the OsmoPrep trials;
9) The **ADVERSE EVENTS** section should include diarrhea as a common AE;
10) The **Electrolyte Changes** subsection of the **ADVERSE EVENTS** section should be moved to the **Electrolyte Changes** subsection of the **CLINICAL STUDIES** section of the label and this subsection should include the percentage of patients who had hyperphosphatemia and hypokalemia in the OsmoPrep trials and the frequencies of reactive hypophosphatemia in other sodium phosphate trials; and
11) The **DOSAGE AND ADMINISTRATION** section of the label should include the recommended amount of clear liquids to be taken with OsmoPrep.

9.5 Comments to Applicant

Please see the Section 1.3.3 (the Safety subsection of the Executive Summary) for the major deficiencies in this NDA. Also see Section 10.2 (the Line-by-Line Labeling Review) for this medical officer's labeling recommendations.

10 APPENDICES

10.1 Review of Individual Study Reports

The individual study reports are in Section 6.1.3.

10.2 Line-by-Line Labeling Review

For this labeling review, words <u>underlined</u> and **bolded** signify an addition and words formatted with a ~~strikethrough~~ indicate a deletion to the sponsor's proposed OsmoPrep label.

097), and did not conduct baseline or post-dose ECGs in their two OsmoPrep studies. In addition, sodium phosphate products have had rare, post-marketing reports of rare ventricular arrhythmias with sodium phosphate use and the serious electrolyte abnormalities associated with OsmoPrep use are known to increase the risk of arrhythmias. The sponsor should refer to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* for further guidance.

This medical officer recommends a second phase 4 commitment to conduct a pharmacokinetic study of OsmoPrep in patients with normal renal function and mild, moderate, and severe renal impairment. This medical officer recommends this study because many post-marketing serious adverse events associated with sodium phosphate colon preparations have occurred in renal insufficiency patients.

9.3.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

9.4 Labeling Review

Since the Division of Medication Errors and Technical Support (DMETS) rejected the sponsor's initial proposed trade name (OsmoPrep), the sponsor has requested approval of trade names for their sodium phosphate bowel preparation in the following order: ——————————
OsmoPrep, and ——). DMETS is currently reviewing the cited trade names.

The following is a summary of the major changes needed in the sponsor's proposed OsmoPrep labeling (please see Section 10.2 for a line-by-line detailed labeling review):

1) The **CLINICAL PHARMACOLOGY** section should included more detailed information about the design, the demographical results, and the pharmokinetic results (phosphate levels) of the pharmacokinetic study. This medical officer believes that the absolute serum phosphate levels should be stated in the label;
2) The **Renal Insufficiency** subdivision of the **Special Populations** subsection of the **CLINICAL PHARMACOLOGY** section should state that patients with mild to moderate renal insufficiency should have laboratory tests (including phosphate, calcium, potassium, sodium, creatinine, and BUN) performed before OsmoPrep administration and post-colonoscopy;
3) The **Geriatric Use** subdivision of the **Special Populations** subsection of the **CLINICAL PHARMACOLOGY** section should state that geriatric patients, compared to younger patients, had higher phosphate levels after sodium phosphate administration;
4) The **CLINICAL STUDIES** section of the label should not include any information regarding secondary endpoints because no multiplicity adjustments were made regarding these endpoints; should define the responses in the primary efficacy scale (Overall Colon Content Cleansing Scale); and should display the amount of concomitant clear liquids used in each treatment group;

32 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Eric Brodsky
3/3/2006 04:24:26 PM
MEDICAL OFFICER

Ruyi He
3/3/2006 05:36:02 PM
MEDICAL OFFICER