CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

MEDICAL REVIEW

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer Review

AUG 29 2000

NDA: 21-097
21-097/S-009
21-097/S-018
21-097/S-025

Sponsor: InKine Pharmaceutical Co., Inc

Drug: Diacol tablets (sodium phosphate monobasic monohydrate + sodium phosphate dibasic anhydrous)

Indication: Cleansing of the Bowel as Preparation for Certain Procedures.

Dates Received by the DGICDP (HFD-180): November 24, 1999, March 22, 2000, May 9, 2000, June 22, 2000, July 27, 2000

Date Received by the Medical Officer: December 6, 1999, March 24, 2000, May 11, 2000, June 23, 2000, July 28, 2000

FDAMA Due Date: September 22, 2000

Date of Draft: August 9, 2000

Medical Officer: Dr. Robert Prizont, MD

Abstract. InKine developed a tablet formulation of 1.5 grams sodium phosphate/sodium biphosphate. InKine seeks approval for the use of tablets as colonic cleansing preparation prior to colonoscopy, in patients 18 years of age or older. The proposed dose, 60 grams=40 tablets, is the dose approved for the use of the buffered Phospho-Soda solution for the same indication. The sponsor submitted results from two Phase III clinical studies. These studies were multi-center, randomized, single-blinded (investigator). The comparator was an approved colonic cleansing PEG solution given as a 4L dose. Patients self-administered the drug preparations. Results showed comparable primary efficacy, quality of colon cleansing, between the two treatments. There was evidenced, reported by the sponsor, of unblinding, by both observers. Patients treated with InKine tablets manifested a higher proportion of hyperphosphatemia, hypocalcemia and hypokalemia. Hypokalemia and hypocalcemia were associated with ECG abnormalities, without serious or overt symptomatology. In some subjects, administration of InKine tablets were associated with alterations of the colonic mucosa. This review details the efficacy and safety of the proposed tablet formulation.

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ON ORIGINAL

Note from the Reviewer. The sponsor has submitted an electronic document (ed) of this NDA. Sections of this clinical review will include sections, subsections, tables or figures, imported unaltered from the submitted ed. This imported electronic data will be abbreviated as (i/ed).

1. Proposed Label.

The following are the INDICATION and DOSAGE proposed for the use of [redacted] tablets *(i/ed)*.

1.1 Indications and Usage

[redacted] Tablets are indicated for cleansing of the bowel when required as a preparation for [redacted] colonoscopy, in adults 18 years of age or older.

1.2 Dosage Administration

The usual adult dosage of [redacted] Tablets for colon cleansing is 40 tablets taken in the following manner:

The evening before the colonoscopy procedure, 3 [redacted] Tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The last dose will be 2 tablets. The day of the colonoscopy procedure, (starting 3-5 hours before the procedure) 3 [redacted] Tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The last dose will be 2 tablets.

Patients are not to repeat this purgative agent within seven days of a previous administration. No additional enema or laxative is required, and patients should be advised NOT to take additional agents, particularly those containing sodium phosphate.

2. Background.

- *This Background section, represents an update and brief summary of colonoscopy, indications for colonoscopy, and use of current bowel cleansing systems, and was created solely by this medical reviewer.*

Since the development of the first fiberoptic colonoscope in 1963[1], and new radiographic and imaging techniques, gastroenterologists and radiologists have used different laxative combinations, e.g., castor oil + milk of magnesia, or various colonic cleansing system in an effort to achieve adequate preparation of the colon. Adequate preparation of the colon prior to colonoscopy is of great relevance for the accurate diagnosis and treatment (excision) of colon polyps and periodic screening of colon cancer. Colon carcinoma is the second leading malignancy in the USA. Each year, 130,000 Americans are diagnosed with cancer of the colon and rectum (colorectal cancer)[2]. Adequate preparation for colonoscopy is similarly important in

Crohn's Disease (CD) and microscopic colitis (collagenous or lymphoid variety), and diagnosis and therapy of unspecified lower gastrointestinal (GI) bleeding[3].

Since its introduction in the early 1980's[4], oral polyethylene-glycol (PEG) electrolyte-balanced solutions [GoLYTELY®, NuLYTELY®, Cherry Flavor NuLYTELY® (Braintree Laboratories), Colyte®, Colyte®-flavored (Schwarz Pharma), and OCL (ABBOTT)] are customarily used as cleansing system to lavage the colon from fecal matter.

The oral buffered salt of monobasic sodium phosphate/dibasic sodium solution (Fleet Phospho®-Soda) is being increasingly used by gastroenterologists as an alternative bowel cleansing regimen in preparing patients for colonoscopy (as well as purgative bowel cleansing system prior to colon x-rays and surgery). This sodium phosphate preparation is available OTC, with a *Professional Label* included in the prescription PDR (Page 1013, 1999 Ed.). Each 5 ml of the flavored Fleet Phospho®-Soda contains 2.4 g of monobasic sodium phosphate monohydrate + 0.9 dibasic sodium phosphate heptahydrate (3.3 grams of sodium phosphate salts), in a stable buffered aqueous solution. The approved purgative dose as a bowel cleansing system for colonoscopy preparation is 90 ml (60 grams), divided in two doses of 45 ml, administered on the evening prior to the procedure, and on the morning of the scheduled colonoscopy. Controlled and uncontrolled clinical investigations, have shown very good to excellent effectiveness, i.e., adequacy of bowel cleansing, with the oral administration of the Fleet Phospho®-Soda buffered solution[5,6,7,8]. However, there have been a number of adverse reactions reported with the oral (and enema) use of the sodium phosphate buffered Fleet solution. The majority of the ADEs are due to electrolyte imbalances in serum, i.e., hypocalcemia, hypokalemia, caused by the sudden increase of serum phosphates. The severity of some reported ADEs, which included deaths, led this Agency to request the sponsor the withdrawal of the large container (240 ml) from the OTC market. The sponsor took action in a Market Withdrawal Letter, *L.A Farrar, C.B. Fleet Co., to Distributors of Phospho-Soda Products, dated May 6, 1993 (included in OTC vol. 090TFM3).* In the Federal Register; March 31, 1994, HHs/FDA , 21 CFR Part 334, (Docket No 78N-036L), this agency added a warning for all sodium phosphate/sodium biphosphate products not to exceed the recommended dosage *(90ml)* unless directed by a doctor.

- In the Safety section of this review, this MO will reference, more in detail, the serious ADEs reported with the use of sodium phosphate/sodium byphosphate as laxatives or purgatives.

Literature Cited by This Medical Reviewer

1. Overhalt BF. Colonoscopy: A review. Gastroenterol, 68:1309-1320, 1975.

2. Colonoscopy, barium enema and polyps. ***HeadlineWatch****, June 19, 2000, cited by http://www.mayohealth.org/mayo/headline/htm/hw000619.htm*

3. Hunt RH et al. Colonoscopy for unexplained rectal bleeding. Gastroent, 76:1158, 1979.

4. Davis GR et al. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. Gastroenterol, 78:991-995, 1980.

4. Davis GR et al. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. Gastroenterol, 78:991-995, 1980.
5. Marshall JB et al. Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-electrolyte lavage for colonoscopy preparation. Gastrointest Endosc, 39:631-634, 1993.

6. Cohen SM et al. Prospective, randomized, endoscopic-blinded trial comparing precolonoscopy bowel cleansing methods. Dis Colon Rectum, 37:689-696, 1994.

7. Henderson JM et al. Single-day, divided-dose oral sodium phosphate laxative versus intestinal lavage as preparation for colonoscopy: efficacy and patient tolerance. Gastrointest Endosc, 42:238-243, 1995.

8. Chilton AP et al. A blinded, randomized comparison of a novel, low-dose, triple regimen with fleet phospho-soda: a study of colon cleanliness, speed and success of colonoscopy. Endoscopy, 32:37-41, 2000.

3. Drug Formulation and Pharmacokinetics.

- *This section of the review will contain very brief information on relevant issues related to formulation and pharmacokinetics. The included paragraphs will be imported from i/ed, or from the biopharmacologist reviewer, without added comments from this medical reviewer.*

1.3 Drug Formulation.

(i/ed from the proposed label with some minor modifications)

Diacol Tablets are white to off-white modified oval compressed tablets, the upper half bisected with a monogram "I" on both sides and the lower half plain. **Each 2.0 gram tablet** contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic anhydrous, USP for **a total of 1.5 grams of sodium phosphate**. Inert ingredients include cellulose, magnesium stearate, and colloidal silicone dioxide. The chemical formula for sodium phosphate monobasic monohydrate, USP is $NaH_2PO_4 \cdot H_2O$. The chemical formula for sodium phosphate dibasic anhydrous, USP is Na_2HPO_4.

1.4 Pharmacokinetics.

(i/ed from the Human Pharmacokinetics and Bioavailability Section submitted by the sponsor, and from the biopharmacology review draft).

Phosphate distributes into plasma and extracellular fluid, cell membranes, and intracellular fluids. Approximately 80% of the total body phosphate exists in the form of hydroxyapatite crystals in bone. In intracellular fluid,

phosphates comprise the principal anion.

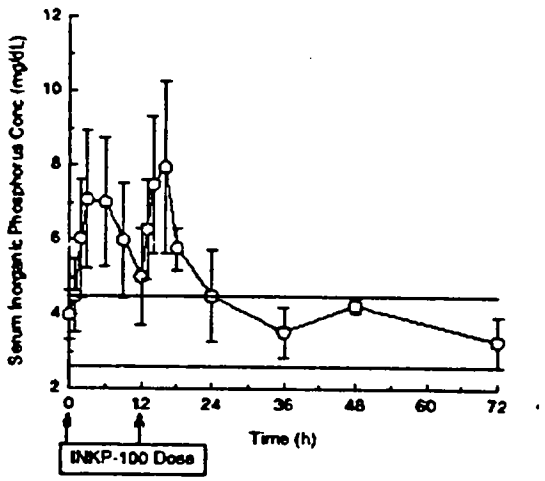
More than 90% of plasma phosphate is filtered and 80% of the filtered phosphate actively reabsorbed in the steady state. Phosphate reabsorption occurs principally in the proximal tubule with a tubular maximum of 0.1 mM/min. Reabsorption is inhibited by parathyroid hormone, resulting in increased renal excretion.

The pharmacokinetics of serum inorganic phosphorus after administration of Diacol have been characterized in one study in healthy volunteers of varying, specified age ranges.

In Study INKP-100-101, 23 healthy volunteers received two 30 g oral doses of Diacol according to the same protocol used by patients prepared for colonoscopy in the clinical trials. Subjects were admitted to the study unit on the morning of Day 1. After a full breakfast, they consumed only clear liquids until noon the following day. The first 30 g dose of Diacol was administered at 6:00 PM on Day 1 (time "0") and the second 30 g dose at 6:00 AM on Day 2. For each dose. Blood samples for measurement of serum inorganic phosphorus [P i] concentrations were collected through 72 hours after the first dose. In addition, serum calcium and potassium concentrations were measured at 18, 48, and 72 hours after the first dose.

Administration of 2 successive oral 30 g doses of Diacol at 6 PM and 6 AM resulted in an increase in serum [P i] above baseline that persisted for approximately 24 hours after the first dose

Figure 1. Mean ± SD Serum Inorganic Phosphorus Concentrations



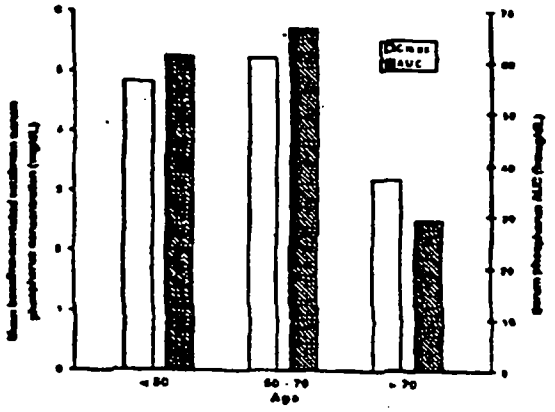
Solid bars (–) represent the lower (2.6 mg/dL) and upper (4.5 mg/dL) lim-

As illustrated in Figure 1, mean serum P i concentrations during this period, although variable, were always within the limits of the normal

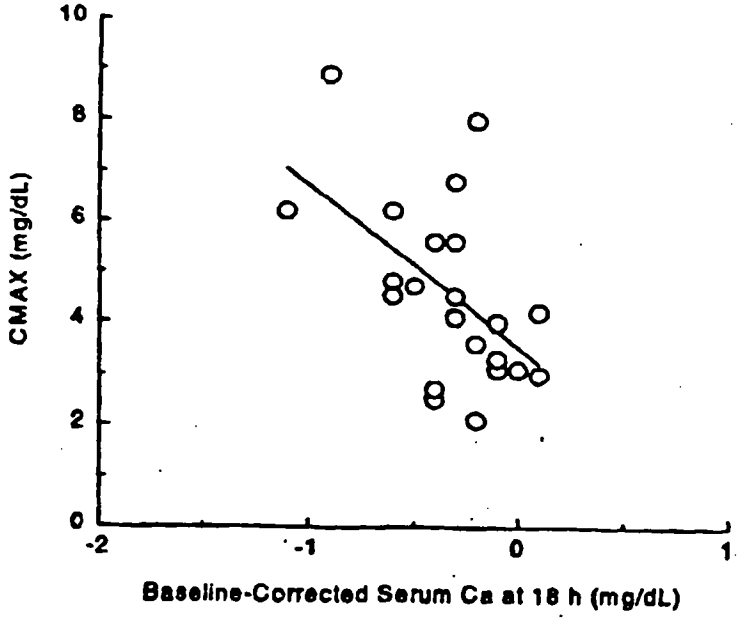
range [redacted] During the 36 hour to 48 hour time period, the majority of subjects had a serum P i concentration that was less than base-line. However, during this period, only 3 of the 23 subjects (13%) had a single serum P i < 2.6 mg/dL and the maximum drop below baseline, 3.1 mg/dL, occurred in a subject whose baseline P i was 5.8 mg/dL.

- *The following 3 graphics and comments were **scanned** from the biopharmacologist reviewer.*

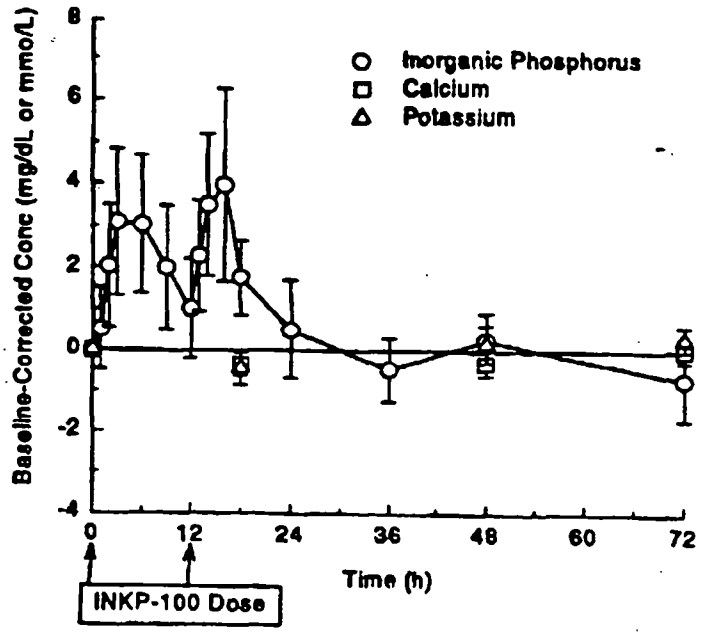
Based on AUC and C_{max} values it appears that absorption of phosphate is reduced in subjects >70 yrs of age following administration of Diacol. But these calculations were based on a small subset of subjects (n = 6).



In the pharmacokinetic study conducted in healthy volunteers, larger increases from baseline in serum phosphorus were associated with larger decreases from baseline in serum calcium. The relationship between serum phosphorus C_{max} and baseline-corrected serum calcium at 18 hr is shown in the following figure.



As shown in the figure below, serum calcium concentrations decreased approximately 0.3 mg/dL from baseline at 18 hrs and 48 hrs and were back to baseline at 72 hrs. Serum potassium levels decreased to 0.4 mmol/L below baseline at 18 hrs and were above baseline at 48 and 72 hrs. Hypokalemia was not observed in any subject in this study. Although one subject experienced a QTc interval that exceeded 450 milliseconds, the increase in QTc intervals (≤ 45 milliseconds) were not considered clinically significant. The mean maximum increase in serum phosphorus concentration was 4 mg/dL above baseline and mean maximum decrease was 1 mg/dL below baseline.



4. Pivotal Clinical Trials.

- *This section will include the relevant information of the Study Protocol and Brief Descriptive of the two Pivotal Clinical Trials 301 and 302. Submitted information identical for 301 and 302 will be included once. The Descriptive of each study will be followed by this Reviewer's Comments (in general, no comments will be made during the Descriptive presentation).*

1.5 Study 301.

This Phase III Pivotal Clinical Study; Protocol titled *"A study of the efficacy and safety of INKP-100 (sodium phosphate tablets) compared with NuLYTELY as a purgative agent for patients undergoing colonoscopic evaluation"*, was initiated October 22, 1998, and completed March 19, 1999. The submitted study report was dated October 28, 1999.

1.5.1 Protocol.

- *Protocol No INKP-100-301.1, was dated January 27, 1999.*

(a) Study Design and Population (*i/ed*). This will be a randomized, single-blinded, multi center (15 centers) study. Approximately 400 eligible patients will be randomized (200 patients per group) to receive receive either Diacol tablets or NuLYTELY.

- The protocol includes the following explanation for the single-blinding:

This study is a single-blind trial, with all investigators being blinded to the bowel-cleansing study product the patients receive. Because of the differences in the products and regimens being compared, a double-blind study would not be practical to per-form. The investigator-blinded design is consistent with studies reported in the medical literature. The necessity of bowel cleansing prior to colonoscopy is well documented, therefore, it would be unethical to use an inactive control (placebo) considering the time, expense, and purpose of colonoscopic procedures. The control group will use an approved study product commonly used for precolonoscopy bowel cleansing administered in the approved dose and dosing regimen.

(b) Study Drugs (*i/ed*).

All eligible patients will be randomized to 1 of the following 2 study product groups:

1. NuLYTELY. 4 L administered orally beginning the afternoon prior to colonoscopy in accordance with its package insert (see NuLYTELY package insert)

2. INKP-100. 30 grams of INKP-100 administered on 2 occasions: the evening prior to and the morning of (3–5 hours before) colonoscopy INKP-100 will be administered as 3 tablets with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets beginning at 6:00 PM on the evening prior to colonoscopy. This schedule will be repeated at 6:00 AM on the morning of colonoscopy (or 3–5 hours before the procedure) when again 3 tablets of INKP-100 will be administered with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. An 8 oz container will be provided. "Clear liquids" include the following: water, ginger-ale, apple juice, weak tea, or other colorless warm or cool liquids.

(c) Inclusion Criteria (*i/ed*). The following were the relevant criteria for study elegibility:

1. Male or female
2. At least 18 years of age
3. Scheduled for colonoscopy
4. Able to swallow tablets without difficulty

(d) Exclusion Criteria (*i/ed*). The following were the relevant exclusion criteria:

1. Acute or chronic renal insufficiency defined as creatinine >2.0 mg/dL
2. Uncontrolled congestive heart failure (American Heart Association Class III or IV) or unstable angina pectoris
3. Ascites
4. Percutaneous transluminal coronary angioplasty (PCTA) within the previous 3 months
5. Myocardial infarction or coronary artery bypass graft surgery within the previous 3 months
6. Electrolyte imbalance including hyponatremia, hyperphosphatemia, or hypocalcemia
7. Experiencing an acute exacerbation of chronic IBD
8. Chronic constipation, defined as fewer than 2 bowel movements per week for a period greater than 1 year
9. Ileus, and/or acute obstruction
10. Ileostomy, right or transverse colostomy, subtotal colectomy with ileosigmoidostomy, or ³50% of colon removed; patients with right or left hemicolectomy only, may be included
11. Hypomotility syndrome, megacolon, idiopathic pseudo-obstruction

(e) Efficacy (*i/ed*). The protocol includes two sections describing the primary efficacy endpoints. Section 3.5.2, *Efficacy and safety measuremants assessment* is in the clinical part of the design. In in this protocol part, Subsection 3.5.2.1., titled in the protocol as *Effectiveness of bowel cleansing*, states the following:

> The effectiveness of the study products will be assessed by a colonoscopist (investigator) directly viewing the colon. Investigators will use a 4-point scale to score the overall quality of colonic cleansing and the quality of cleansing of the ascending colon. In addition, investigators will record the presence or absence of the following: bleeding (and if present, assign a cause), superficial mucosal aphthous ulcerations, and undigested or partially digested white INKP-100 tablets.
>
> Patient tolerance of the study-product regimens will be assessed by completion of a self-administered, standardized patient questionnaire. In addition, patients will be asked to observe and record whether undigested or partially digested white tablets appear in their bowel movements during the bowel cleansing..

The *Statistical and analytical plans* section (4.1) states the following:

> The *primary efficacy variable*—overall quality of colonic purgation—will be measured using a 4-point scale. The equivalence in quality of colonic purgation between the 2 study-product groups will be assessed using 2 one-sided t-tests. Each of the 2 t-tests will have a null hypothesis of a 0.3-point difference between study-product groups and an alternative hypothesis of no difference.

The *secondary efficacy variables* of the study are whether the procedure needed to be redone, the quality of colonic purgation in the ascending colon, and patient tolerance (satisfaction).

The quality of colonic purgation in the ascending colon will be measured using the same 4-point scale as the overall quality of colonic purgation. The same method will be used to assess the equivalence of the 2 study-product groups. An analysis will be conducted on the answers to a patient tolerance (satisfaction) questionnaire to determine what aspects of patient tolerance are related to study product.

An exploratory instrument consisting of a visual analog scale will be com-pared to the 4-point scale used above. Characteristics of this instrument will be determined and will be compared to the 4-point scale used above.

(f) Relevant Safety (*i/ed*).

All patients must demonstrate laboratory values within normal limits for inclusion in this clinical study. During the study, abnormal blood urea nitrogen (BUN) and creatinine values will be reported as adverse events. In addition, the following abnormal laboratory values will be reported as adverse events if they occur in association with a clinical event (including changes in the ECG):

sodium: ≤135 or ≥152 mEq/L
potassium: ≤3.5 or ≥5.0 mEq/L
bicarbonate: ≤22 or ≥30 mEq/L
calcium: ≤8.0 or ≥10.6 mg/dL
inorganic phosphorus: ≤2.0 or ≥8.6 mg/dL
magnesium: ≤1.3 or ≥2.5 mg/dL

A 12-lead ECG will be performed at the Screening Visit, Visit 1, and Visit 2. All ECGs will be read by a central reviewer.

1.5.2 Descriptive

- This section will describe only the relevant results of this pivotal trial. Most of the descriptive text will be taken directly from **i/ed**. All **tables or figures will be scanned from i/ed**. Disposition of Patients

A total of 432 patients were randomized to receive study product; 216 patients to receive INKP-100 and 216 patients to receive NuLYTELY. Ten patients were discontinued from the study prior to treeatment with study product (*3 patients randomized to the INKP-100 treatment group and 7 patients randomized to the NuLYTELY treatment group*). The remaining **422 patients were treated with study product**; 213 patients were treated with INKP-100 and 209 patients were treated with NuLYTELY.

Ninety-eight percent of treated patients had an assessment of colonic cleansing following study product administration. There were no differences between treatment groups with respect to the percentage of patients who had an assessment of colonic cleansing.

The disposition of the 432 patients randomized is illustrated in the following sponsor's Table 1.1.

Table 1.1
Disposition of Patients
(All Randomized Patients)
InKine Pharmaceutical Company, Inc.
Protocol INKP-100-301

	Treatment Groups	
	INKP-100 60 gas (N=216)	NuLYTELY (N=216)
Enrolled Patients Completed (n,%)	(205, 94.9%)	(203, 94.0%)
Discontinued (n,%)	(11, 5.1%)	(13, 6.0%)
Lack of Efficacy*	(1, 0.5%)	(1, 0.5%)
Adverse Event	(4, 1.9%)	(0, 0.0%)
Intercurrent Illness	(0, 0.0%)	(1, 0.5%)
Entrance Violation	(0, 0.0%)	(1, 0.5%)
Protocol Violation	(0, 0.0%)	(1, 0.5%)
Withdrew Consent	(2, 0.9%)	(3, 1.4%)
Investigator Medical Decision	(0, 0.0%)	(0, 0.0%)
Sponsor Discontinued Study	(0, 0.0%)	(0, 0.0%)
Lost to Follow-up	(1, 0.5%)	(3, 1.4%)
Other	(3, 1.4%)	(3, 1.4%)

1.5.2.1 Demographics.

The following table shows that All Randomized Patients (ARP), had no differences in age, sex, race, or weight . Between 92% to 95% of randomized patients complained of gastrointestinal symptoms.

Patient Population	ARP	
Parameter	INKP-100 (n=216)	NuLYTELY (n=216)
Age (years)		
Mean	56.4	56.7
Range	19–84	18–82
Age Group – n (%)		
< 55	94 (43.5)	88 (40.7)
55 - <65	56 (25.9)	58 (26.9)
65 - <75	46 (21.3)	51 (23.6)
> = 75	20 (9.3)	19 (8.8)
Gender – n (%)		
Males	112 (51.9)	101 (46.8)
Females	104 (48.1)	115 (53.2)
Race –n (%)		
Caucasian	195 (90.3)	183 (84.7)
African-American	14 (6.5)	21(9.7)
Native American	1 (0.5)	0 (0.0)
Asian	0 (0.0)	3 (1.4)
Hispanic	5 (2.3)	8 (3.7)
Other	1 (0.5)	1 (0.5)
Weight (pounds)		
Mean	185.1	181.8
Range	113–313	95–325

1.5.2.2 Efficacy

Initially, the sponsor had performed the efficacy in the All-Assessed-Patients (AAP). This population was the subset of 415 patients who completed all assessments (Diacol= 208; NuLYTELY=207).

According to the protocol and presented data, the primary efficacy was the comparison between the two groups in the investigators assessment of colon cleansing, scored on 4-point visual scale. Based on this scale *Excellent* = 1, *Good* = 2, *Fair* = 3, and *Inadequate* = 4. The following is the descriptive of each rating, taken from the CRF sample, included in the protocol.

1. Excellent: >90% of mucosa seen, mostly liquid stool, minimal suction needed for adequate visualization

2. Good: >90% of mucosa seen, mostly liquid stool, significant suctioning required for adequate visualization

3. Fair: >90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed

4. Inadequate/reprep: <90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

The initial primary efficacy analysis done by InKine was comparison of the **Primary Efficacy** in the AAP population. **This AAP analysis excluded 27 randomized patients; of which 17 were randomized and treated with experimental drug**. This Inkine analysis on AAP population showed **no** overall difference between Diacol and NuLYTELY. Hence, the sponsor states that ***The difference between treatments in the over-all quality of colonic purgation was not statistically significant for the all assessed patient population. The mean score for patients who received INKP-100 was 1.80 compared to a mean score of 1.82 in patients who received NuLYTELY.***

In the next step, the sponsor proceeded to compare the rating distribution with colonoscopy cleansing, i.e., *Excellent, Good, Excellent + Good*. The sponsor states the following:

There was no statistically significant difference between treatment groups with respect to the distribution of designated colonic cleansing rating (see Ta b l e 8). Overall physician ratings of colonic purgation were Excellent or Good in 82.2% of patients who received INKP-100 and 75.4% of patients who received NuLYTELY. When the number of designated Excellent and Good ratings were combined and compared to the Fair or Inadequate groups, no significant difference was observed between treatments with respect to the overall distribution of physician responses.
InKine Table 8 is shown below (*scanned*).

Table 8. Quality of purgation in All Assessed Patients (%) by treatment group

	Treatment Groups		
Parameter	INKP-100 (n=208)	NuLYTELY (n=207)	NuLYTELY-INKP-100
Mean quality of colonic purgation score (SD)	1.80 (0.76)	1.87 (0.83)	0.02
Confidence interval			(-0.14, 0.17)
p-value			0.4311
Overall bowel preparation			
Excellent or Good	171 (82.2)	156 (75.4)	
Fair	34 (16.3)	49 (23.7)	
Inadequate (required re-preparation)	3 (1.4)	2 (1.0)	
p-value			0.1661

This Division requested to have an analysis of primary efficacy in the All-Randomized-Patients (**ARP**) and 422 All-Treated-Patients (**ATP**) . In these analysis, patients who were excluded in the AAP were considered (*imputed*) to have either an *Excellent* score, or alternatively, an *Inadequate* score. According to InKine Table 9 (*Page 54, Clinical Report of 301*), the ARP and ATP revealed no differences between the two drugs, in the investigators rating of colonic cleansing. InKine Table 9 is shown below (*scanned*).

Table 9. Imputed mean scores for the ATP and ARP groups

	ATP		ARP	
Quality of colonic purgation	**INKP-100**	**NuLYTELY**	**INKP-100**	**NuLYTELY**
Number of patients	213	209	216	216
Results imputed to Excellent, score = 1				
Mean score	1.78	1.81	1.77	1.78
(SD)	(0.76)	(0.83)	(0.76)	(0.83)
p-value	0.3753		0.4518	
Results imputed to Inadequate, score = 4				
Mean score	1.85	1.84	1.88	1.91
(SD)	(0.82)	(0.85)	(0.85)	(0.92)
p-value	0.5834		0.3932	

Inkine submitted the results of the *Secondary Efficacy* variables, i.e., rating by investigators of ascending colon cleansing and drug acceptance. The following InKine Table 11 (*scanned*), shows the ascending colon cleansing assessment in the ATP. There were no differences between the treatment groups.

Table 11. Analysis of quality of colonic purgation in the ascending colon – All Assessed Patients

	Treatment Groups		
Parameter	**INKP-100 (n=208)**	**NuLYTELY (n=207)**	**NuLYTELY-INKP-100**
Mean quality of colonic purgation in the ascending colon score (SD)	1.89 (0.80)	1.79 (0.83)	-0.09
Confidence interval			(-0.25, 0.07)
p-value			0.8702
Ascending colon preparation			
Excellent or Good	153 (76.1)	155 (76.0)	
Fair	45 (22.4)	47 (23.0)	
Inadequate (required re-preparation)	3 (1.5)	2 (1.0)	
p-value			0.8897

InKine described the following about drug tolerance (*i/ed*):

> Significantly more INKP-100 patients reported that they were able to take all the study medication, 92.8% of those who received INKP-100 as compared to 57.3% of those who received NuLYTELY. More patients who received INKP-100 tablets found it "easy" to take the study product than did the patients who received NuLYTELY liquid, 60.0% versus 29.0%, respectively. Of those patients taking INKP-100, 73.7% reported the tablets to have "no taste", whereas 88.9% of patients who received NuLYTELY reported the taste to be "not good, but tolerable", "bad, barely tolerable" or "very bad, not tolerable". A greater percentage of patients who received INKP-100 indicated a preference for taking the same preparation in the future compared to patients who received NuLYTELY.

The next InKine Table 7.0, displays drug preference of patients, and **compliance**:

Table 7.0
Patient Questionnaire
(All Treated Patients)
InKine Pharmaceutical Company, Inc.
Protocol INKP-100-301

	Treatment Groups		
	INKP-100 60 gms (N = 213)	NuLYTELY (N = 209)	p-value
Able to Take All Study Preparation? (n, %)*			
Yes	(194, 92.8%)	(118, 57.3%)	<0.0001
No	(15, 7.2%)	(88, 42.7%)	
Of Those Answering No, How Much Left? (n, %)**			
Less than 1/4	(8, 57.1%)	(51, 55.4%)	0.5202
1/4 to 1/2	(3, 21.4%)	(30, 32.6%)	
More than 3/4	(3, 21.4%)	(11, 12.0%)	
How Easy/Difficult to Take? (n, %)**			
Easy	(128, 60.0%)	(60, 29.0%)	<0.0001
Slightly Difficult	(63, 30.0%)	(63, 30.4%)	
Moderately Difficult	(17, 8.1%)	(65, 31.9%)	
Extremely Difficult	(4, 1.9%)	(18, 8.7%)	
How Did Study Preparation Taste? (n, %)**			
No Taste	(154, 73.7%)	(23, 11.1%)	<0.0001
Not Good, But Tolerable	(53, 25.4%)	(142, 68.6%)	
Bad, Barely Tolerable	(2, 1.0%)	(36, 17.4%)	
Very Bad, Not Tolerable	(0, 0.0%)	(6, 2.9%)	
How Easy to Drink Clear Liquids? (n, %)**			
Easy	(159, 77.2%)	(57, 27.5%)	<0.0001
Slightly Difficult	(31, 15.0%)	(74, 35.7%)	
Moderately Difficult	(14, 6.8%)	(53, 25.6%)	
Extremely Difficult	(2, 1.0%)	(23, 11.1%)	

Patients who took study product but may or may not have had a colon assessment.
*p-value is from the Fisher's Exact Test.
**p-value is from the Cochran-Mantel-Haenszel Test.
***Among these patients, the p-value represents the comparison between patients who in the future would prefer tablets to those who would prefer liquid.
Percentages are based on patients completing responses.
NA = Not Applicable.

1.5.2.3 Reviewer's Comments.

i. The data analyses of this pivotal clinical study met the study protocol main objective, to show comparable efficacy in the primary efficacy endpoint, *overall quality of colonic cleansing*, between InKine's Diacol tablets and the chosen comparator, Braintree's NuLYTELY buffered solution. The data show comparability in cleansing efficacy in comparisons of the three different patient populations, the ARP, ATP, and the AAP. To achieve clinical comparability, or statistical equivalence, InKine used the comparison of **events, mean of quality of colonic quality,** measured by visual score rated from 1 *(Excellent)* to 4 (*Inadequate*). In the *Integrated Summary of Efficacy (Pages 17-20)*, the sponsor justifies the use of this visual score by means of an in-house validation of this method by an appointed panel of five gastroenterologists. These five gastroenterologists evaluated the quality of colon cleansing in videotapes of 80 patients. Four different questionnaires were used to rate the quality of colon cleansing. The four included the 1 to 4 rating used in this 301 trial. Out of the four questionnaires, only one (*Questionnaire 3*) showed a good inter-rater reliability, this questionnaire was *"chosen for use in each of the clinical trials"*. This reviewer requested from InKine to reanalize the results using the proportion of patients with *Excellent, Good, Fair*, or *Inadequate* preparation. Using this approach in the AAP, there were more *Excellent* ratings in the NuLYTELY and statistically more *Good* ratings in the Diacol group, i.e., Diacol had 38.9% *Excellent* (81/208) and 43.3 % *Good* (90/208), vs.44% *Excellent* NuLYTELY (91/207 and 31.4 % *Good* (65/207). This potential inter-observer variability in the use and interpretation of visual 4 point score rating, underlines the problematic of its use in assessing objective evidence of primary efficacy. Noteworthy to point out, only 3 Diacol patents and 2 NuLYTELY (1-1.5% of patients assessed) were considered to have an *Inadequate* (Failure) colonic preparation by any analyses used. In the view of this reviewer, a simpler approach, comparison of **proportion of patients** with *Adequate* or *Inadequate* colonic cleansing, might have provided a better assessment of efficacy.

ii. The lack of protection might have impacted the efficacy results of the trial. According to the protocol, the investigators were blinded. Patients were unblinded. The study medication, e.g., preparation of 4 L NuLYTELY solution was deferred to the unblinded observer, the patient. Over 90% of the patients on Diacol tablets took the entire dose, 40 large tablets, 2 grams in weight each, for a total of 80 grams tablets. Instead, only 57% of the patients allocated to prepare and self-administer the 4 L NuLYTELY buffered solution, took the prospectively established 4 L dose. Approximately, 12-30 % of patients assigned to **cherry-flavored** NuLYTELY, took only between ¼ to ½ of the total 4 L PEG buffered solution (attributed to *salty taste*). The lack of blinding protection has its origin in the design of the pivotal trials. In the rationale (see *Protocol*) for the use of sodium phosphate/sodium biphosphate tablets, InKine argues that the two approved customarily used colonic cleansing systems, PEG solutions (GoLYTELY, NuLYTELY) and flavored Fleet Buffered Phospho-Soda (sodium phosphate/sodium biphosphate solution), induce nausea. Paradoxically, instead of choosing the natural control-comparator, i.e., 45 ml b.i.d., Phospho-Soda buffered solution, InKine selected the 4L PEG solution. The InKine choice of 4 L PEG solution, cancelled the possibility of blinding. Had InKine chosen the flavored Buffered Phospho-Soda (sodium/sodium

biphosphate buffered solution), administered bid, i.e., 45 ml dose PM (3 tablespoons), and another 45 ml dose AM (3 tablespoons), both doses followed by ½ glass of water, the blinding could have been certainly attainable.

1.6 Study 302.

This second Phase III Pivotal Clinical Study had an initiation date of November 24, 1998, and a completion date of March 29, 1999. This submitted study report was dated October 29, 1999.

1.6.1 Protocol

*Title, design, and date of this Protocol INKP-100-302, are **identical** to Protocol No INKP-100-301.1 (the reader is referred to Protocol INKP-100-301.1, for consultation of content).*

1.6.2 Descriptive

- *This section will describe only the relevant results of this pivotal trial. Most of the descriptive text will be taken directly from i/ed. All **tables or figures will be scanned from i/ed.***

1.6.2.1 Disposition of Patients

A total of **454 patients were randomized** to receive study product; **229 patients to receive INKP-100 and 225 patients to receive NuLYTELY**. Subsequently, **17 patients were discontinued from the study** prior to treatment with study product (**15 patients randomized to the INKP-100** treatment group and **2 patients randomized to the NuLYTELY** treatment group).

The remaining **437 patients were treated with study product**; **214** patients were treated **with INKP-100** and **223** patients were treated **with NuLYTELY**.

The disposition of ATP is illustrated in InKine Table 2 (*scanned*).

Table 2. Disposition of All Treated Patients (ATP)

	Treatment Groups		
	Total	INKP-100	NuLYTELY
Treated patients	437 (100)	914 (100)	223 (100)
Had assessment of colonic cleansing	430 (98.4)	212 (99.1)	218 (97.8)
Completed the study	427 (97.7)	209 (97.7)	218 (97.8)
Discontinued from the study	10 (2.3)	5 (2.3)	5 (2.2)
Lack of efficacy	2 (0.5)	2 (0.9)	0 (0.0)
Adverse event	4 (0.9)	1 (0.5)	3 (1.3)
Withdrew Consent	2 (0.5)	1(0.5)	1 (0.4)
Other	2 (0.5)	1(0.5)	1 (0.4)

1.6.2.2 Demographics

The following InKine Table 3 shows the demographics in the ARP. There were no differences between treatment groups in age, sex, race, and weight.

Patient Population	ARP	
Parameter	INKP-100 (n=229)	NuLYTELY (n=225)
Age (years)		
Mean	56.3	57.5
Range	21–83	25–83
Age Group – n (%)		
< 55	108 (47.2)	97 (43.1)
55 - <65	45 (19.7)	46 (20.4)
65 - <75	51 (22.3)	56 (24.9)
> = 75	25 (10.9)	26 (11.6)
Gender – n (%)		
Males	107 (46.7)	110 (48.9)
Females	122 (53.3)	115 (51.1)
Race - n (%)		
Caucasian	198 (86.5)	194 (86.2)
African-American	12 (5.2)	20 (8.9)
Asian	0 (0.0)	1 (0.4)
Hispanic	19 (8.3)	10 (4.4)
Weight (pounds)		
Mean	182.5	183.8
Range	[redacted]	

1.6.2.3 Efficacy

Initially, Inkine compared the **Primary Efficacy**, in the AAP subset. InKine stated:

Differences between treatments in the overall quality of colonic purgation was not statistically significant for the all assessed patient population. *The mean score for patients who received INKP-100 was 1.69 compared to a mean score of 1.80 in patients who received NuLYTELY.*

Within each category, assessments designated as Excellent, Good, Fair or Inadequate for colon cleansing were similar between treatment groups. There was no statistically significant difference between treatment groups with respect to the distribution of designated colonic cleansing rating (see Table 8). Overall physician ratings of colonic purgation were Excellent or Good in 86.3% of patients who received INKP-100 and 78.0% of patients

who received NuLYTELY. When the number of designated Excellent and Good ratings were combined and compared to the Fair or Inadequate groups, no significant difference was observed between treatments with respect to the overall distribution of physician responses.

The next InKine Table 8 (*scanned*), shows the results of colonic cleansing, in the AAP population.

Table 8. Quality of purgation in All Assessed Patients (%) by treatment group

	Treatment Groups		
Parameter	INKP-100 (n=212)	NuLYTELY (n=218)	NuLYTELY-INKP-100
Mean quality of colonic purgation score (SD)	1.69 (0.74)	1.80 (0.81)	0.11
Confidence interval			(-0.03, 0.26)
p-value	0.0642		
Overall bowel preparation			
Excellent or Good	183 (86.3)	170 (78.0)	
Fair	26 (12.3)	45 (20.6)	
Inadequate (required re-preparation)	3 (1.4)	3 (1.4)	
p-value	0.0650		

In the next analyses, InKine displays the Primary Efficacy results in the ATP and ARP populations. For each patient population, InKine imputed discontinued patients as either having a rating of (1) *Excellent*, or (2) *Inadequate*. Noticeable are the paradoxical results of these imputations in the ARP population. The imputation of discontinued patients as *Excellent* resulted in significant superiority of the InKine Diacol. Imputation of discontinued patients as *Inadequate* resulted in almost identical rating score, i.e., Diacol = 1.86; NuLYTELY = 1.87. **Implicit in this paradoxical results is the impact of marked imbalance in randomized but prematurely discontinued patients, i.e., Diacol = 15, NuLYTELY = 2.**

The Primary Efficacy results in the ATP and ARP population is displayed in the next InKine Table 9 (*scanned*).

Table 9. Imputed mean scores for the ATP and ARP groups

Quality of colonic purgation	ATP		ARP	
	INKP-100 (n=214)	NuLYTELY (n=223)	INKP-100 (n=229)	NuLYTELY (n=225)
Results imputed to Excellent, score = 1				
Mean score (SD)	1.68 (0.74)	1.78 (0.81)	1.64 (0.73)	1.78 (0.81)
p-value		0.0841		0.0269
Results imputed to Inadequate, score = 4				
Mean score (SD)	1.71 (0.77)	1.85 (0.87)	1.86 (0.94)	1.87 (0.88)
p-value		0.0357		0.4496

Ratings by investigators of the efficacy (*secondary*) of Diacol and NuLYTELY on the adequacy of ascending colon cleansing showed no differences between the two treatment groups (AAP). The lack of difference between treatment groups in cleansing of the ascending colon is illustrated in the next InKine Table 11.

Table 11. Analysis of quality of colonic purgation in the ascending colon – All Assessed Patients

Parameter	Treatment Groups		
	INKP-100 (n=211)	NuLYTELY (n=216)	NuLYTELY-INKP-100
Mean quality of colonic purgation in the ascending colon score (SD)	1.80 (0.80)	1.80 (0.90)	0.00
Confidence interval			(-0.15, 0.16)
p-value	0.4538		
Ascending colon preparation			
Excellent or Good	172 (81.5)	163 (75.5)	
Fair	35 (16.6)	48 (22.2)	
Inadequate (required re-preparation)	4 (1.9)	5 (2.3)	
p-value	0.3126		

InKine submitted results of drug tolerance (*secondary efficacy variable*) in the ATP population. InKine states the following (*i/ed*):

> Significantly more INKP-100 patients reported that they were able to take all the study medication, 95.3% of those who received INKP-100 as

compared to 57.2% of those who received NuLYTELY. More patients who received INKP-100 tablets found it "easy" to take the study product than did the patients who received NuLYTELY liquid, 56.1% versus 30.1%, respectively. Of those patients taking INKP-100, 68.7% reported the tablets to have "no taste", whereas 93.5% of patients who received NuLYTELY reported the taste to be "not good, but tolerable", "bad, barely tolerable" or "very bad, not tolerable". A greater percentage of patients who received INKP-100 indicated a preference for taking the same preparation in the future compared to patients who received NuLYTELY.

The next Table InKine Table 7.0, shows patient preferences, and **compliance**:

Table 7.0
Patient Questionnaire
(All Treated Patients)
InKine Pharmaceutical Company, Inc.
Protocol INKP-100-302

	Treatment Groups		
	INKP-100 80 gms (N = 214)	NULYTELY (N = 223)	p-value
Able to Take All Study Preparation? (n, %)*			<0.0001
Yes	(204, 95.3%)	(123, 57.2%)	
No	(10, 4.7%)	(92, 42.8%)	
Of Those Answering No, How Much Left? (n, %)**			0.4727
Less than 1/4	(8, 85.7%)	(81, 64.9%)	
1/4 to 1/2	(1, 14.3%)	(21, 22.3%)	
More than 3/4	(0, 0.0%)	(12, 12.8%)	
How Easy/Difficult to Take? (n, %)**			<0.0001
Easy	(119, 56.1%)	(66, 30.1%)	
Slightly Difficult	(65, 30.7%)	(69, 31.5%)	
Moderately Difficult	(21, 9.9%)	(54, 24.7%)	
Extremely Difficult	(7, 3.3%)	(30, 13.7%)	
How Did Study Preparation Taste? (n, %)**			<0.0001
No Taste	(145, 68.7%)	(14, 6.5%)	
Not Good, But Tolerable	(64, 30.3%)	(145, 66.8%)	
Bad, Barely Tolerable	(2, 0.9%)	(46, 21.2%)	
Very Bad, Not Tolerable	(0, 0.0%)	(12, 5.5%)	
How Easy to Drink Clear Liquids? (n, %)**			<0.0001
Easy	(143, 68.6%)	(81, 37.0%)	
Slightly Difficult	(49, 23.6%)	(73, 33.3%)	
Moderately Difficult	(13, 6.3%)	(36, 16.4%)	
Extremely Difficult	(3, 1.4%)	(29, 13.2%)	

*p-value is from the Fisher's Exact Test.
**p-value is from the Cochran-Mantel-Haenszel Test.
***Among those patients, the p-value represents the comparison between patients who in the future would prefer tablets to those who would prefer liquid.
Percentages are based on patients completing responses.
NA = Not Applicable.

1.6.2.4 Reviewer's Comments.

i. As in Study 301, this pivotal clinical study 302 showed comparable primary efficacy, i.e., quality of colonic cleansing, between Diacol 60 g (40 tablets), and 4 L cherry flavored PEG buffered solution (Braintree NuLYTELY). The apparent borderline significant superiority of Diacol over NuLYTELY of the AAP comparison, is not acceptable, because it is driven by the imbalance in randomized and prematurely discontinued patients. As stated in the descriptive, 15 Diacol patients versus only 2 NuLYTELY subjects were randomized and discontinued from the trial. Inclusion as failures of these prematurely discontinued patients in the ARP analysis, resulted in almost identical overall scores, i.e., Diacol = 1.86; NuLYTELY = 1.87.

ii. The same concerns about the lack of blinding protection expressed in my comments of Study 301, apply for this Study 302. Noteworthy, the proportion of subjects **not** taking the required 4 L NuLYTELY in this Study 302 was **identical** as the proportion of patients not taking the required 4 L NuLYTELY in Study 301, i.e., **57%**.

5. Safety

- *This section will describe the Integrated Summary of Safety, as presented by the sponsor. This reviewer will include only relevant parts of this section. The summary of all relevant parts the descriptive submitted by InKine, will be followed by this Reviewer Comments.*

1.7 Population.

Included in this Descriptive, will be the safety of the **427 subjects treated with 60 grams Diacol in Pivotal Clinical Trials 301 and 302** (432 subjects were treated with NuLYTELY), the safety of **98 subjects treated with Diacol in the dose-ranging Phase II Study 201**, in which 29 subjects received Diacol 60 grams (no NuLYTELY control), and the **23 human volunteers treated with Diacol 60 grams in the Pharmacokinetic Phase I Study** (no NuLYTELY control). Hence, this represents an overall safety **review of 548 subjects treated with Diacol** tablets, of which **479 subjects received 60 grams** (40 tablets).

The mean age of subjects was 56 years (18-84), there were slightly more women than men, (52% to 48%), the majority were Caucasian (86%); the largest proportion of African-American was 9% in Study 302. At baseline, the majority of subjects enrolled in the trials had GI complaints (>80%); 47-52% had some medical finding related to the cardiovascular system. In the pivotal trials, there were more patients with musculoskeletal and genitourinary problems randomized to NuLYTELY (52% and 53%, respectively), than Diacol (46%, and 47.5 %, respectively).

1.8 Serious Adverse Events.

There no deaths in any of the studies. The sponsor states that "*there were no SAEs reported in studies 101 or 201. While there were 4 SAE reports submitted during the Phase III program (see Table 7). 2 of the patients had not taken study product at the time of the event and another patient was a case of colon cancer found during colonoscopy*". InKine's Table 7, *scanned* from the ISS, is shown below. The only serious AE related to drug by the investigator, was Subject 10813, randomized to Diacol. This subject developed a *de novo* atrial fibrillation after the first dose, and was hospitalized. The narrative of this subject (*i/ed*), is included after Table 7.

Table 7. Serious adverse events

Classification Treatment	Patient ID	Age (yr) Gender Race	Serious adverse event	Comments
Classification I No study product taken	INKP-100-301 10638	52 Male African-American	Hospitalized for small bowel obstruction	The patient was not randomized and did not take study product. The event was characterized as severe and unrelated to study product. (see 10638 narrative)
Classification I No study product taken	INKP-100-301 11134	56 Female Pacific Islander	Hospitalized for acute exacerbation of chronic asthma	The patient was randomized (to NuLYTELY) but never took study product. The event was characterized as severe and unrelated to study product. (see 11134 narrative)
Classification II Diacol taken	INKP-100-301 10813	50 Male Caucasian	Hospitalized for atrial fibrillation	The event occurred after first dose of 30 g Diacol. The event was considered moderate in severity and probably related to study product. (see 10813 narrative)
Classification III Diacol taken	INKP-100-301 11511	82 Male Caucasian	Colon cancer found at colonoscopy resulting in hospitalization for treatment of cancer	Reported as an SAE due to hospitalization for surgical referral. The event was considered moderate in severity and unrelated to study product. (see 11511 narrative)

Patient 301-08-13, a 50-year old Caucasian male, had a history of asthma (last reported use of prn Primatene® 2 days prior to colonoscopy), allergies, possible colitis, degenerative joint disease, mild hypothyroidism, mononucleosis and acne; no cardiovascular history was noted. The laboratory values and ECG were normal at Screening for study 301. He took the 30 g evening dose of Diacol and experienced nausea, profuse vomiting and a rapid irregular heartbeat shortly thereafter. Per investigator recommendation, he drove himself to the emergency room and was diagnosed with new-onset atrial fibrillation. He denied chest pain, shortness of breath and excessive intake of alcohol or caffeine. The only abnormal blood chemistries were high sodium of 150 mEq/L (normal range: 137-145 mEq/L) and high phosphorus of 5.1 mg/dL (normal range: 2.5-4.4 mg/dL). He converted to normal sinus rhythm after a single infusion of ibutilide fumarate in saline and was admitted overnight for telemetry evaluation. He remained stable, with no further

episodes of nausea or vomiting and no evidence of acute myocardial infarction, and was discharged the following day. Stress test evaluation several days later was normal with no evidence of underlying cardiac disease. The patient was discontinued from the study due to the hospitalization prior to the second dose of Diacol and before undergoing colonoscopy. The investigator characterized the vomiting as moderate and probably related to study drug and the atrial fibrillation as moderate and probably related to study drug.

1.8.1 Medical AE in ≥ 1% of Subjects

The sponsor text included bloating, nausea, and headaches as emergent events. According to the sponsor, there were a significantly larger proportion of NuLYTELY subjects who experienced, bloating, nausea, and vomiting. This is illustrated in the next InKine Table 9, *scanned* from the ISS (Page 42).

Table 9. Clinical treatment emergent adverse events - number (%) of All Treated Patients (adverse events occurring in ≥1% of patients in All Diacol group)

	Diacol				
Body System & COSTART term	All Patients (n=548)	60 g Studies 101, 201, 301 & 302 (n=481)	60 g Studies 301 & 302 (n=427)	NuLYTELY Studies 301 & 302 (n=432)	p- value*
Any adverse events	526 (96.0)	459 (95.4)	405 (94.8)	407 (94.2)	0.7647
Body as a Whole	296 (54.0)	266 (55.3)	250 (58.5)	301 (69.7)	0.0008
Bloating	231 (42.2)	213 (44.3)	201 (47.1)	269 (62.3)	<0.0001
Pain abdominal	143 (26.1)	135 (28.1)	133 (31.1)	158 (36.6)	0.0976
Headache	27 (4.9)	19 (4.0)	14 (3.3)	12 (2.8)	0.6952
Digestive	197 (35.9)	178 (37.0)	162 (37.9)	254 (58.8)	<0.0001
Nausea	181 (33.0)	165 (34.3)	153 (35.8)	234 (54.2)	<0.0001
Vomiting	46 (8.4)	41 (8.5)	39 (9.1)	79 (18.3)	0.0001
Neurological	14 (2.6)	13 (2.7)	12 (2.8)	10 (2.3)	0.6721
Dizziness	8 (1.5)	8 (1.7)	7 (1.6)	5 (1.2)	0.5763

1.9 Withdrawals Due to Adverse Events

There were 10 subjects withdrawn from the studies due to adverse events. One of these subjects was the described Subject 10813, enrolled in Study 301, and discontinued due to the development of atrial fibrillation after 30 g Diacol. One patient was withdrawn because of a rash. The reason for withdrawal of the other 8 subjects was nausea, vomiting, abdominal pain,

diarrhea. Noteworthy, in spite that the sponsor revealed a higher proportion on NuLYTELY developing nausea and vomiting, 6 of the 8 withdrawals for nausea, bloating, vomiting, or abdominal pain were Diacol subjects. Only 2 NuLYTELY subjects were withdrawn because of nausea, bloating, vomiting, or abdominal pain. This is illustrated in InKine Table 8 (*scanned*), Pages 38-39, InKine ISS.

Table 8. Withdrawals due to adverse events - All Treated Patient population

Patient ID	Treatment	Age (yr) Gender Race	Adverse event	Comments
INKP-100-301 10813	Diacol 60 g	50 Male Caucasian	SAE - Hospitalized for atrial fibrillation	The event occurred after the first dose of 30 g Diacol. The event was considered moderate in severity and probably related to study product (see 10813 narrative)
INKP 100-201 112	Diacol 60 g	78 Female Caucasian	Explosive diarrhea, nausea, rectal irritation	The AEs occurred shortly after the first dose of 30 g Diacol. Explosive diarrhea and rectal irritation were characterized as moderate in severity; nausea as mild. All were considered as probably related to study product. (see 112 narrative)
INKP-100-201 229	Diacol 60 g	49 Female Caucasian	Vomiting	The AE occurred after the first dose of 30 g Diacol. Vomiting was characterized as severe and probably related to study product. (see 229 narrative)
INKP-100-301 10106	Diacol 60 g	76 Female Caucasian	Nausea, vomiting	The AEs occurred shortly after the first dose of 30 g Diacol. Nausea and vomiting were characterized as moderate in severity and probably related to study product. (see 10106 narrative)
INKP-100-301 11205	Diacol 60 g	74 Female Caucasian	Abdominal cramping, bloating	The AEs occurred after the first dose of 30 g Diacol. Abdominal cramping and bloating were characterized as severe and probably related to study product. (see 11205 narrative)
INKP-100 302 21905	Diacol 60 g	71 Female Caucasian	Vomiting	The AE occurred after a partial first dose of 24 g Diacol. Vomiting was characterized as mild and probably related to study product. (see 21905 narrative
INKP-100-302 20410	NuLYTELY	70 Male Caucasian	Rash	Undocumented amount of NuLYTELY taken. Rash developed the same day. It was characterized as moderate in severity and possibly related to study product. (see 20410 narrative)

InKine Table 8 continues in the next page.

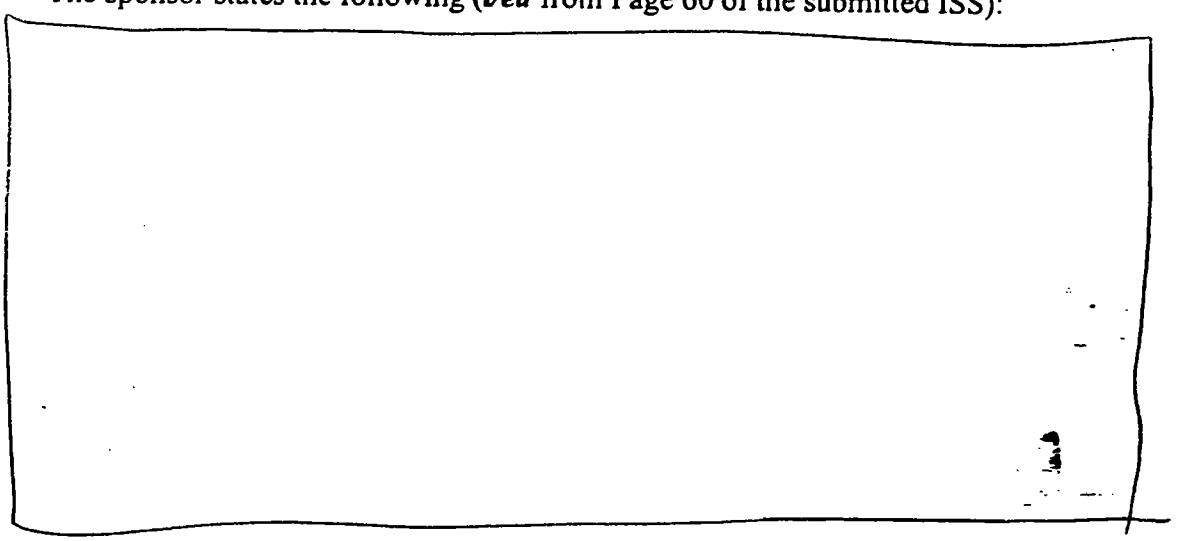
Table 8. Withdrawals due to adverse events - All Treated Patient population (Continued)

Patient ID	Treatment	Age (yr) Gender Race	Adverse event	Comments
INKP-100-302 20923	NuLYTELY	80 Male Caucasian	Abdominal pain, bloating, nausea	Estimated 15 oz. of NuLYTELY taken. AEs began shortly after the first dose. Abdominal pain was characterized as mild; nausea and bloating as severe. All AEs were considered probably related to study product. (see 20923 narrative)
INKP-100-302 21606	NuLYTELY	36 Female Caucasian	Vomiting, nausea, bloating	Estimated 31 oz. of NuLYTELY taken. AEs began after the first dose. Nausea and vomiting were characterized as severe; bloating as mild. All AEs were considered probably related to study product. (see 21606 narrative)
INKP-100-201 232	Diacol 60 g	71 Male Caucasian	Nausea	This patient was erroneously reported as having discontinued due to an adverse event. This patient completed the study, but only took the evening dose of Diacol. For completeness, a narrative is included (see 232 narrative)

1.10 Laboratory Adverse Events in the All Treated Patient Population.

In the 3 efficacy studies conducted by InKine (studies INKP-100-201, INKP-100-301, INKP-100-302), blood was drawn to determine serum calcium, phosphorus, sodium, potassium, chloride, bicarbonate and magnesium concentrations at baseline/screening, at the time of colonoscopy (Visit 1, approximately 18 hours after the first dose of Diacol, and 3-5 hours after the second dose in Diacol treated patients), and at the follow-up visit (Visit 2, 2-3 days after colonoscopy). Blood sample analyses were performed at a central laboratory.

The sponsor states the following (***i/ed*** from Page 60 of the submitted ISS):



InKine Table 23 is shown below (*scanned* from Page 61, submitted ICC).

Table 23. Treatment emergent adverse events in serum chemistry- number (%) of All Treated Patients (adverse events occurring in ≥1% of patients in the All Diacol group)

Body System & COSTART term	Diacol			NuLYTELY Studies 301 & 302 (n=432)	Diacol 60 g (301/302) vs NuLYTELY p-value
	All Patients (n=548)	60 g Studies 101, 201, 301 & 302 (n=481)	60 g Studies 301 & 302 (n=427)		
Any adverse events	526 (96.0)	459 (95.4)	405 (94.8)	407 (94.2)	
Metabolic/Nutritional	475 (86.7)	408 (84.8)	357 (83.6)	291 (67.4)	<0.0001
Hypochloremia	194 (35.4)	173 (36.0)	166 (38.9)	172 (39.8)	
Hypokalemia	176 (32.1)	171 (35.6)	156 (36.5)	38 (8.8)	<0.0001
Hyperphosphatemia	173 (31.6)	107 (22.2)	73 (17.1)	0 (0.0)	<0.0001
Alkalosis (increased bicarbonate)	131 (23.9)	114 (23.7)	87 (20.4)	81 (18.8)	
Hypocalcemia	101 (18.4)	70 (14.6)	54 (12.6)	2 (0.5)	<0.0001
Hypophosphatemia	84 (15.3)	75 (15.6)	62 (14.5)	4 (0.9)	<0.0001
Acidosis (decreased bicarbonate)	83 (15.1)	80 (16.6)	79 (18.5)	62 (14.4)	
Hyponatremia	75 (13.7)	63 (13.1)	40 (9.4)	53 (12.3)	
Hypervolemia (decreased BUN, creatinine)	56 (10.2)	55 (11.4)	54 (12.6)	51 (11.8)	
Hyperglycemia	16 (2.9)	2 (0.4)	0 (0.0)	0 (0.0)	
BUN increase	13 (2.4)	11 (2.3)	10 (2.3)	12 (2.8)	
Hyperkalemia	11 (2.0)	9 (1.9)	7 (1.6)	24 (5.6)	0.0028
Creatinine increase	9 (1.6)	6 (1.2)	5 (1.2)	11 (2.5)	

1.10.1 Laboratory Changes of "potential clinical concern "

At the request of this Division, InKine submitted *a comparison of the upper and lower limits of the normal range and the values identified as of* ***"potential clinical concern"***. The normal serum lower and upper levels of phosphorus, calcium, potassium, and sodium was provided by InKine in Table 28. The table also includes the serum values of these electrolytes, considered of *"potential clinical concern"*.

Table 28. Comparison of laboratory normal range and defined values of "potential clinical concern"

Lab parameter (units)	Normal Range		Potential Clinical Concern	
	Lower	Upper	Lower	Upper
Phosphorus (mg/dL)	2.4	4.7	≤2.0	≥8.6
Potassium (mEq/L)	3.5	5.1	≤3.5	≥5.0
Sodium (mEq/L)	138	148	≤135	≥152
Calcium (mg/dL)	8.6	10.4	≤8.0	≥10.6

In the next paragraphs, InKine describes the following proportion of patients on Diacol and NuLYTELY with serum levels of phosphorus, calcium, potassium, sodium, of *potential clinical concern*. The text was ***i/ed***, Pages 74-75, ISS (highlighted text was done by this reviewer).

Inorganic phosphorus - **After dosing (Visit 1), 13.8% of patients in the All Diacol group had inorganic phosphorus values that exceeded the upper threshold for "potential clinical concern" compared with none of the NuLYTELY group.** At Visit 2 (48-72 hours later), 12.7% of the All Diacol group were below the lower threshold for "potential clinical concern" for this parameter compared to 1.0% of NuLYTELY-treated patients. The patient with atrial fibrillation had a slightly elevated phosphorus value (5.1 mg/dL) at the time of evaluation and was discharged with a phosphorus value of 4.8 mg/dL.

Calcium - **In the All Diacol group, 10.1% of patients had calcium values below the lower threshold for "potential clinical concern" at Visit 1 versus 0.2% of NuLYTELY-treated patients.** Values remained below the lower threshold at Visit 2 in 1.2% of the All Diacol group and none of the NuLYTELY group. None of these patients had an adverse event associated with these changes in calcium values. The patient who experienced atrial fibrillation did not have hypocalcemia at the time of the event.

Potassium - **At Visit 1, 31.9% of the All Diacol group had potassium values that were below the lower threshold for "potential clinical concern" compared with 4.2% of the NuLYTELY group.** Potassium values in 3.5% of NuLYTELY-treated patients were above the upper threshold for "potential clinical concern" at Visit 1 compared to 0.8% of the All Diacol-treated group. At Visit 2, values were below the lower threshold for "potential clinical concern" in 5.1% of the All Diacol group and 3.5% of the NuLYTELY group; approximately 2.0% of patients in both groups had values that exceeded the upper threshold for "potential clinical concern". No adverse events were associated with changes in potassium values.

Sodium - Values for sodium were below the lower threshold for "potential clinical concern" at Visit 1 in 1.4% of the All Diacol group and 2.7% of

the NuLYTELY group. More patients were below the lower threshold for "potential clinical concern" at Visit 2 in the All Diacol-treated group (6.4%) and NuLYTELY group (5.9%).

InKine concludes the following:

These data in nearly 500 patients on Diacol 60 g do not indicate a risk of adverse events as a result of transient changes in serum electrolytes. InKine does not believe that these transient changes represent a clinical problem. **This position is supported by the many years of experience with Fleet Phospho-Soda at a dose that provides the same amount of sodium phosphate as Diacol Tablets.**

1.11 Electrocardiogram (ECG) Results

ECGs were obtained for all patients at baseline, Visit 1 and Visit 2 in studies 301 and 302. Twelve-lead electrocardiograms were obtained at baseline, at the time of colonoscopy (3-5 hours after the second 30 g dose in patients receiving Diacol), and at a follow-up visit 2-3 days after colonoscopy (Visit 2). For studies 301 and 302, the baseline ECG occurred up to one week prior to Visit 1. In study 101, ECGs were obtained at baseline, immediately prior to ingesting Diacol (Day 1, time 0), 18 hours after initial dosing.

A copy of the ECG was kept at the investigative site and a copy was sent to [redacted] for evaluation. Consistent with protocol design, routine ECGs were not obtained in study 201, but, at the discretion of the investigator, could be performed if clinically indicated. Therefore, the analysis of ECGs presented in this section includes ECGs obtained in studies 101, 301 and 302.

In order to be consistent with identification of changes and interpretation of the ECG, the ECG was evaluated (read) at a central location using a worksheet collaboratively developed by InKine and [redacted] A single, board-certified cardiologist who was a practicing electrophysiologist, made the final interpretation of each ECG while blinded to the treatment assignment. Throughout the studies, the blinded central reader compared each ECG to the baseline ECG and reported the evaluation as "no change, improved, or deteriorated".

Mean heart rate, QT c , QT, QRS and PR intervals were calculated from each ECG. As shown in Ta b l e 3 3 , the change in mean heart rate or PR interval in either Diacol- or NuLYTELY-treated patients was insignificant. **In the Diacol 60 g group (301 and 302), the mean increase in QT c (16.6 msec) and QT (11.5 msec) at Visit 1 were significantly greater than the QT c (6.8 msec) and QT (4.9 msec) mean changes in the NuLYTELY group.** At Visit 2 were comparable to baseline values in all treatment groups.

InKine Table 33 is shown below (*scanned* from Page 94, ISS).

Table 33. Mean change from baseline in ECG parameters

ECG Parameter (normal range)	Diacol		NuLYTELY	Comparison of Diacol 60 g from 301 and 302 with NuLYTELY
	All Patients 60 g Studies 101, 301 & 302 (n=450)	60 g Studies 301 & 302 (n=427)	Studies 301 & 302 (n=432)	p-value*
Heart rate (bpm) (50-100 bpm)				
Baseline	70.0	70.4	70.6	
Visit 1	1.2	1.3	0.3	
Visit 2	1.4	1.2	1.1	
QT_c (msec) (<479 msec)				
Baseline	401.6	401.6	401.2	
Visit 1	15.7	16.6	6.8	<0.0001
Visit 2	1.8	2.2	0.6	
QT (msec) (none)				
Baseline	374.9	373.7	372.9	
Visit 1	11.2	11.5	4.9	0.0003
Visit 2	-2.2	-1.2	-2.4	
QRS (msec) (<119 msec)				
Baseline	86.9	86.9	87.0	
Visit 1	0.2	0.3	-0.6	
Visit 2	0.1	0.1	-0.5	
PR (msec) (≥260 msec)				
Baseline	160.1	160.1	161.6	
Visit 1	1.0	0.7	-0.2	
Visit 2	-0.1	-0.2	-0.4	

Source: Section 16.2.56 through Section 16.2.60

* Analysis of variance comparing INKP-100 60 g (studies 301 and 302 combined) to NuLYTELY

1.11.1 ECG Associated with Serum Electrolyte Abnormalities.

(a) The next InKine Table 37, Page 101, ISS, illustrates the proportion of ECG abnormalities, **other than QT prolongation**, that were associated with electrolyte abnormalities (*scanned*). InKine *states that the majority of ECG abnormalities associated with electrolyte abnormalities occurred in Diacol patients because they had a higher incidence of electrolyte abnormalities.*

Table 37. ECG abnormalities associated with serum electrolytes - Number (%) of all treated patients (occurring in >1% of patients in any treatment group studies 301 and 302)

ECG Abnormality and Serum Analyte	Diacol 60 g (n=427)	NuLYTELY (n=432)
Total number (%) patients with any ECG abnormality	98 (22.9)	84 (19.4)
Hypophosphatemia* (≤2.0 mg/dL)	62 (14.5)	6 (1.4)
Any ECG abnormality†	8 (12.9)	1 (16.7)
Depressed ST wave	5 (8.1)	0 (0.0)
Flat T wave	5 (8.1)	0 (0.0)
Hyperphosphatemia* (≥8.6 mg/dL)	63 (14.8)	0 (0.0)
Any ECG abnormality†	15 (23.8)	0 (0.0)
Depressed ST wave	8 (12.7)	0 (0.0)
Flat T wave	5 (7.9)	0 (0.0)
Hypokalemia* (≤3.5 mEq/L)	160 (37.5)	40 (9.3)
Any ECG abnormality†	47 (29.4)	12 (30.0)
Depressed ST wave	18 (11.2)	4 (10.0)
Flat T wave	16 (10.0)	1 (2.5)
1st degree heart block	6 (3.8)	0 (0.0)
Hyperkalemia* (≥5.0 mEq/L)	30 (7.0)	32 (7.4)
Any ECG abnormality†	9 (30.0)	7 (21.9)
Depressed ST wave	4 (13.3)	0 (0.0)
Hypocalcemia* (≤8.0 mg/dL)	51 (11.9)	1 (0.2)
Any ECG abnormality†	12 (23.6)	1 (100)
Flat T wave	6 (11.8)	0 (0.0)
Hyponatremia* (≤135 mEq/L)	60 (14.4)	72 (16.7)
Any ECG abnormality†	8 (13.3)	22 (30.6)
Depressed ST wave	1 (1.7)	7 (9.7)
Flat T wave	2 (3.3)	5 (6.9)

Source: Section 16.2.82 through Section 16.2.91

* Percent of total number of patients in treatment group
† Percent of total number of patients with designated electrolyte abnormality

(b) Subsequent to the initial submission, the Division requested from InKine to provide a **correlation between prolonged QT intervals and serum electrolyte changes**. The Division cut-off for prolonged QT interval was established at > 450 milliseconds (ms). There were 75 patients in whom a prolonged QT interval was associated with changes in serum electrolytes. Seventy four (99%) were patients enrolled in pivotal trials 301 and 302. Out of this 74 patients, 50 (68%) were in the Diacol group, whereas 24 (32%) were in the NuLYTELY group.

InKine assigned Dr. Raymond Woosley, M.D., Ph. D., from the Department of Pharmacology at the Georgetown Medical Center, to perform a correlation between prolonged QT intervals using

the Bazzet correction (QTc) and changes in serum electrolytes. The next Table 3 (Amendment of June 23, 2000), show the differences in ECG changes in the Diacol and NuLYTELY patients (*scanned*).

Table 3 – Changes in QTc and Selected Serum Electrolytes in the Pivotal Trials by Treatment Group

	Diacol (n=427)			NuLYTELY (n=432)		
	Baseline	Mean Change at Visit 1	Mean Change at Visit 2	Baseline	Mean Change at Visit 1	Mean Change at Visit 2
QTc (msec)	401.6	16.6	2.2	401.6	6.8	0.6
K (mEq/L)	4.2	-0.6	-0.1.	4.2	-0.1	-0.1
Ca (mg/dL)	9.1	-0.5	-0.1	9.1	-0.1	-0.1
Mg (mg/dL)	1.9	0.0	0.0	1.9	0.0	-0.1

Dr Woosley noted that [as expected] ***correlation's were found between serum in serum K and Ca and the QT_c at Visit 1 in patients who took Diacol***. Dr. Woosley concluded the following (*scanned* from the submitted text):

> These findings suggest that changes in serum levels of K and Ca are the most important cause of QT interval prolongation following Diacol administration. The temporal pattern of QT the data also support this conclusion: by Visit 2, when the electrolytes were essentially back to baseline, the QTc behaved likewise.

1.12 Colonoscopic Finding of Mucosal Aphtous Ulcerations.

In the first paragraph of this safety issue, InKine states the following (***i/ed***, highlighted by this reviewer)

Sodium phosphate enemas, known to cause proctoscopic and histologic abnormalities of the distal sigmoid colon and rectum, are typically avoided in patients undergoing colonoscopy. **The appearance of aphthoid-like mucosal lesions has recently been reported in patients who took oral sodium phosphate solution for colonoscopy preparation.**

InKine reports the following incidence of colonic mucosal ulceration observed in the Phase III trials 301 and 302:

The incidence of mucosal ulceration following doses of Diacol less than 60 g was approximately 3 percent. In the two large studies, the incidence of reported mucosal ulceration following **60 g of Diacol was 8.0 and 8.7 percent**, compared to **4.3 and 1.4 percent in the NuLYTELY** group.

The number and proportion of patients with mucosal apthous ulcerations, diagnosed at colonoscopy, are shown in Table 1 (*scanned from the Pharmacology/Toxicology section*). The data included 2 subjects enrolled in the Phase II Study 201. These subjects developed mucosal aphtous ulcerations after treatment with Diacol tablets, 24 grams and 48 grams, respectively.

Table 1. Number (%) of patients in each study with reported superficial mucosal ulcerations

		Diacol Dose			
Study number	**Number of patients**	**24 g**	**48 g**	**60 g**	**NuLYTELY**
201	Total	34	33	29	N/A
	With mucosal ulceration (%)	1 (2.9)	1 (3.0)	0 (0)	N/A
301	Total	N/A	N/A	208	207
	With mucosal ulceration (%)	N/A	N/A	18 (8.7)	9 (4.3)
302	Total	N/A	N/A	212	218
	With mucosal ulceration (%)	N/A	N/A	17 (8.0)	3 (1.4)

1.13 Reviewer Comments

My comments will focus on the three most relevant safety findings associated with administration of 60 grams Diacol as colon cleansing system,, namely, (i) serum electrolyte imbalances, (ii) ECG changes, and (iii) development of mucosal aphtous ulcerations.

i. As reported with Phospho-Soda solution, subjects treated with Diacol, 60 gram tablets experienced a sharp increase in serum phosphate, and a concomitant decrease in serum calcium and potassium. Hence, **36 % of all subjects treated with Diacol 60 g had hypokalemia** (versus 9% NuLYTELY), **22 % developed hyperphosphatemia** (versus 0 % NuLYTELY). The hyperhosphatemia was higher in females, Caucasian, in subjects with lower creatinine clearance, and low serum inorganic phosphorus (Page 79, InKine ISS). The hyperphosphatemia was associated with **hypocalcemia in 15% of subjects treated with Diacol** (versus 0.5 % NuLYTELY). Electrolyte imbalances associated with administration of sodium phosphate/sodium biphosphate have been reported in the literature[1,2,3], and, potentially, it is a safety risk. In a recent review by the Office of Postmarketing Drug Risk Assessment (OPDRA), 13 fatal outcomes were reported with a mean administration of 90 ml of sodium monophosphate/sodium biphosphate solution. This Phospho-Soda solution dose is equivalent to the 60 grams sodium monophosphate/sodium biphosphate contained in the InKine tablets. The majority of these reported fatal outcomes occurred in elderly subjects, and were due or associated to either refractory hypocalcemia, or hypokalemia. The March 31, 1994 Federal Register

cited by InKine (see my *Background* section, this review) reported 5 fatal outcomes due to intake of Phospho-Soda solution.

ii. The reported ECG abnormalities associated with electrolyte disturbances could have relevant implications on potential drug interactions. Hence, the sponsor reported that QT prolongation was correlated to hypokalemia and hypocalcemia. There are a number of drugs which may cause QT prolongation, leading to serious cardiac arrhythmia's, i.e., torsades de pointes, and even death. The entire list of drugs with potential to cause QT prolongation is too large to be detailed in this review, but it includes antiarrythmics, e.g., quinidine; antibiotics, e.g., eythromycin; antidepressants, e.g., amitriptyline; antifungals, e.g., ketoconazole; antipsychotics, e.g., sertindole; protease inhibitors, e.g., indinavir. The only serious ADR related by the investigator to an experimental drug, was a *de novo* development of atrial fibrillation in a 50 y man who took first 30 grams of the Diacol tablet dose. Although the reported serum electrolytes only revealed hyperphosphatemia and hypernatremia, free serum ionic calcium concentration, and intracellular-extracellular shift of this electrolyte and potassium are unknown variables which might have influenced the development of the cardiac arrhythmia.

iii. The colonic development of mucosal aphtous ulcerations reported in up to 9 % of patients administered the Diacol 60 g tablets, has similarly been reported in the literature in patients given Phospho-Soda (NaP) solution[4,5,6]. The ulcers appear to be small (1 to 3 mm), aphtous in appearance. Zwas et al found colonic mucosal ulcers in 25% (13/53) of patients given Phospho-Soda solution versus 2% (1/44) observed in patients given a PEG colonic cleansing lavage. The authors concluded that because of the potential for misinterpretations of these ulcers in patients with IBD, they do not recommend the use of NaP colonic cleansing preparations when the diagnosis of IBD is suspected. My review of the CRF of patients reported with apthous ulcerations in these InKine trials, revealed similar misinterpretations from several investigators. Histology and histochemistry of the colonic mucosa in patients given NaP cleansing solutions revealed active cell proliferation and increase in the mitotic labeling index , including proliferation within these aphtous ulcers.

References Cited by the Reviewer.

1. Di Palma JA et al. Biochemical effects of oral sodium phosphate. Dig Dis Sci, 41:749-753, 1996.

2. Escalante CP et al. Hyperphosphatemia associated with phosphorus-containing laxatives in apatient with chronic renal insufficiency, http://www.sma.org/smj/97feb17.htm.

3. Fass R et al. Fatal hyperphosphatemia following fleet phospho-soda in a patient with colonic ileus. Am J Gastroenterol, 88:929-932, 1993.

4. Hixson LJ. Colorectal ulcers associated with sodium phosphate catharsis. Gastrointestinal Endosc, 42:101-102, 1995.

5. Zwa FR et al. Colonic mucosal abnormalities associated with oral sodium phosphate solution. Gastrointestinal Endosc, 43:463-466, 1996.

6. Driman DK et al. Colorectal inflammation and increased cell proliferation associated with oral sodium phosphate bowel preparation solution. Hum Pathol, 29:972-978, 1998.

6. Executive Summary, Conclusion, and Recommendations for Regulatory Actions.

The following are my brief summaries of efficacy and safety:

1.14 Executive Summary of Efficacy.

To support the efficacy claim of NaP/Na2P tablets, as colonic cleansing system for colonoscopy preparation, InKine performed two pivotal Phase III, multi center clinical trials, Studies 301 and 302. As control comparator, InKine selected one of the approved colonic cleansing systems, a PEG buffered preparation (NuLYTELY ®), which requires administration of 4 L. The trials were randomized, but single-blinded (investigator). Patients self-administered the Diacol tablets or PEG solution. The night before of the procedure they took 20 tablets = 30 grams NaP/Na2P or the 4L NuLYTELY The morning of the procedure, those patients who were allocated to Diacol, self-administered another dose of 20 Tablets = 30 g. Each trial was prospectively designed to randomized 200 subjects on each treatment arm. Trials 301 and 302 randomized 445 patients to Diacol and 441 to NuLYTELY. Each trial randomized app. 8% to 15% additional patients in each treatment. In trial 302, 15 Diacol versus 2 NuLYTELY patients were randomized and subsequently prematurely discontinued. Primary Efficacy was prospectively established as the quality of colonic cleansing, as rated by investigator on a visual analogue score, ranging from 1=Excellent to 4=Inadequate. The overall results of Primary Efficacy analysis for the AAP, ATP, and ARP population revealed comparable quality of colonic cleansing between Diacol and NuLYTELY, i.e., scores ranging from 1.70 to 1.80. There was wide inter-observer variation in interpretation and use of visual scores by investigators. Further, there was overt evidence of unblinding of both observers, investigators-gastroenterologists, and patients. This break of blinding is displayed in the next two InKine tables. Table 14, *scanned* from InKine ISE, shows that > 50% of investigators became unblinded to Diacol, by the visualization of *"undigested white tablets"*. In addition, physicians made comments of potential unblinding in 25% of CRFs from Diacol patients, versus 4% of similar comments in CRFs from NuLYTELY patients. Combined, there were reasons for potential unblinding in 81% of Diacol patients, versus 14% of NuLYTELY patients. In Table 15, InKine reports that the overt unblinding did not hamper the comparability of primary efficacy scores. Although the efficacy of the Diacol tablets as colonic cleansing system may have been demonstrated, the lack of blinding protection, cast serious doubts about the real or apparent validity of the visual scores, and the significance of statistical analysis. Similarly, the unblinding may have canceled any claim of superiority of Diacol over NuLYTELY, including tolerance and compliance, at least in the view of this medical reviewer.

Table 14. Reasons for potential investigator unblinding

Reason for potential unblinding*	Treatment group		
	Diacol (n=420)	NuLYTELY (n=425)	Total (n=845)
Presence of undigested white tablets on colonoscopy	216	24	240
Physician aware of treatment group	8	8	16
Patient disclosed study product	14	10	24
Physician comments on Case Record Form suggested potential unblinding†	103	18	121
Total Reasons	341	60	401
Total Patients	256 (61%)	46 (11%)	302 (36%)

* Some patients had more than 1 reason for potential unblinding
† Most often related to presence of whitish residue in colon

Table 15. Mean score for overall colon cleansing in patients with and without indicia of potential investigator unblinding - Studies 301 and 302

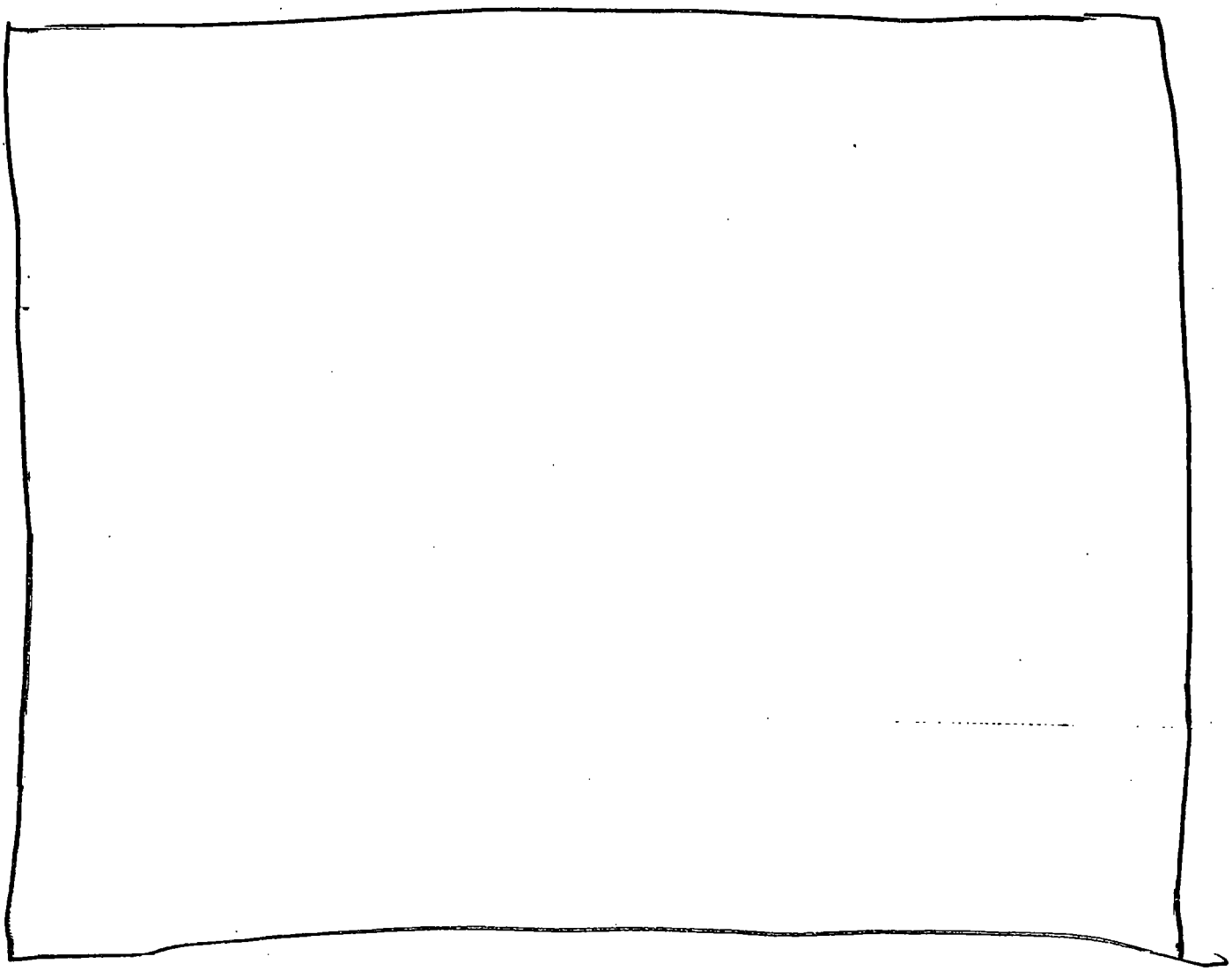
	Patients without potential unblinding		Patients with potential unblinding		All patients	
	Diacol	NuLYTELY	Diacol	NuLYTELY	Diacol	NuLYTELY
Number of patients (%)	164 (39)	379 (89)	256 (61)	46 (11)	420 (100)	425 (100)
Mean score (SD)	1.76 (0.81)	1.80 (0.82)	1.74 (0.71)	1.89 (0.82)	1.75 (0.75)	1.81 (0.82)
95% confidence interval of the mean scores	(1.64-1.88)	(1.72-1.88)	(1.65-1.83)	(1.65-2.13)	(1.68-1.82)	(1.73-1.89)

1.15 Executive Summary of Safety

The safety data included patients enrolled in Phase III Studies 301 and 302, those enrolled in the dose-ranging Phase II Study 201, and normal subjects enrolled in the Pharmacokinetic Study 101. Those populations encompassed a total of 548 subjects treated with Diacol and 479 subjects treated with NuLYTELY. There were three safety issues of concern, shown in patients treated with Diacol, i.e., serum electrolyte imbalances, ECG changes, and development of colonic mucosal ulcerations. About 32 % of patients treated with 60 g Diacol developed

hypokalemia (versus 4 % of the PEG comparator) in values considered as *potential clinical concern*. Similarly, 10% of patients developed very low levels of serum calcium. ECG tracings revealed that ECG abnormalities were associated with serum electrolyte imbalances. These abnormalities were more noticeable in women, and Caucasian. Based on the experience with the Fleet Phospho-Soda solution, electrolyte abnormalities may be dangerous in the elderly, in whom several fatal outcomes related to ingestion of the NaP solution have been reported. There was a close correlation of hypokalemia and hypocalcemia with prolongation of the QT interval. This finding constitutes a risk to some patients, e.g., those with unknown prolongation of QT intervals, and subjects taking drugs which are known to prolong the QT interval. The colonic mucosal aphtous ulcerations seen in Diacol patients have been reported in subjects treated with NaP solutions. Potentially, these iatrogenic ulcerations may be a confounding variable in IBD.

Based on the efficacy and safety of InKine Diacol Tablets, **I conclude** that (a) the Phase III trials have shown evidence of efficacy of Diacol tablets for cleansing system for preparation of colonoscopy, (b) the Phase II trials had severe breaches in blinding, and that this lack of adequacy cancels any claim of superiority over the PEG comparator, and (c) there are serious safety issues that need to be clearly addressed in the label.



1 page(s) of revised draft labeling has been redacted from this portion of the review.

[redacted]

/S/

Robert Prizont. M D.

cc:
NDA 21-097
HFD-180
HFD-180/STalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-181/AKacuba
HFD-180/JChoudary
HFD-180/LZhou
f/t 8/25/00 jgw

Concur. 25, 2000

/S/ /S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-097 **CHEMEMISTRY REVIEW #:** 1 **REVIEW DATE:** 04/24/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11/23/1999	11/23/1999	12/02/1999
Amendment (BZ)	12/28/1999	12/30/1999	12/30/1999
Amendment (BC)	01/06/2000	01/07/2000	01/10/2000
Amendment (BC)	02/10/2000	02/11/2000	02/18/2000
Amendment (BC)	03/14/2000	03/15/2000	03/20/2000
Amendment (BZ)	03/29/2000	03/30/2000	04/06/2000

NAME & ADDRESS OF APPLICANT:

InKine Pharmaceutical Company, Inc.
Sentry Park East
1720 Walton Road
Blue Bell, Pennsylvania 19422

DRUG PRODUCT NAME:

Proprietary:	Diacol TM
Nonproprietary/USAN:	Sodium Phosphate Monobasic (USP) Sodium Phosphate Dibasic Anhydrous (USP)
Code Name/#:	INKP-100
Chem.Type/Ther.Class:	7/S

PHARMACOLOGICAL CATEGORY: Purgative

INDICATION: Cleansing of the bowel when required as a preparation for certain diagnosis procedure, such as colonosocopy, in adults 18 years of age or older.

DOSAGE FORM: Solid Oral Dosage

STRENGTH: 2.0 mg tablets

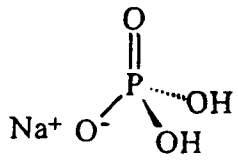
ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: √ Rx ___ OTC

Special Product: ___ Yes √ No

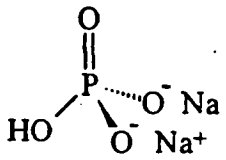
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Sodium Phosphate Monobasic (USP)



Molecular Formula: $NaH_2PO_4.H_2O$
Molecular Weight: 137.99

Sodium Phosphate Dibasic Anhydrous (USP)



Molecular Formula: Na_2HPO_4.
Molecular Weight: 141.96

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

DMF Number and Type	Item referenced	Holder	Status	Review Date and Reviewer's Name	Letter Date

RELATED DOCUMENTS (if applicable): None

CONSULTS:
Dissolution to Biopharmaceutics (pending)
Nomenclature to OPDRA (pending)

APPEARS THIS WAY
ON ORIGINAL

REMARKS/COMMENTS:

During the reviewing process of the NDA, the applicant has submitted following amendments:

- Amendment dated December 28, 1999. This amendment contains the initial release data, including dissolution, for the three validation batches of Diacol.
- Amendment dated January 06, 2000, which contains certificate of analysis for 3 Diacol clinical batches.
- Amendment dated February 10, 2000. This amendment contains certificate of analysis for 3 Diacol validation batches [redacted]
- Amendment dated March 14, 2000. This amendment contains an addendum to the pharmaceutical development report.
- Amendment dated March 29, 2000, which contains stability data for the [redacted] time points.

General Comment about this NDA (Diacol tablets)

Diacol active ingredients (sodium phosphate monobasic and sodium phosphate dibasic) have been used in an OTC marketed drug product solution called Fleet Phospho-Soda. Therefore, the formulation is the major difference change between Diacol tablets and the marketed drug product. Fleet Phospho-Soda solution.

Comment regarding investigational formulation

[redacted]

CONCLUSIONS & RECOMMENDATIONS:

The NDA is Approvable from the Chemistry, Manufacturing and Control point of view, however, the NDA applicant should provide additional information delineated in the draft letter at the end of this review.

/S/ 05/11/00
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 5/11/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA # 21-970
HFD-180/L.Talarico
HFD-180/Div File/NDA # 21-970
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
HFD-181/A.Kucuba
R/D Init by:

KH-CM-09

JUL - 3 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-097 **CHEMEMISTRY REVIEW #:** 2 **REVIEW DATE:** 07/03/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (BC)	06/01/00	06/05/00	06/09/00
Amendment (BZ)	06/06/00	06/08/00	06/13/00
Amendment (C)	06/22/00	06/23/00	02/28/00

NAME & ADDRESS OF APPLICANT:

InKine Pharmaceutical Company, Inc.
Sentry Park East
1720 Walton Road
Blue Bell, Pennsylvania 19422

DRUG PRODUCT NAME:

Proprietary:	Diacol TM
Nonproprietary/USAN:	Sodium Phosphate Monobasic (USP) Sodium Phosphate Dibasic Anhydrous (USP)
Code Name/#:	INKP-100
Chem.Type/Ther.Class:	7/S

PHARMACOLOGICAL CATEGORY: Purgative

INDICATION: Cleansing of the bowel when required as a preparation for certain diagnosis procedure, such as colonosocopy, in adults 18 years of age or older.

DOSAGE FORM: Solid Oral Dosage

STRENGTH: 2.0 mg tablets

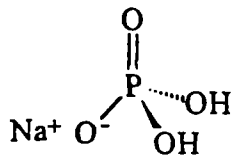
ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx √ OTC ___

Special Product: Yes √ No ___

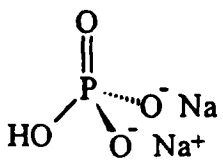
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Sodium Phosphate Monobasic (USP)



Molecular Formula: $NaH_2PO_4.H_2O$
Molecular Weight: 137.99

Sodium Phosphate Dibasic Anhydrous (USP)



Molecular Formula: Na_2HPO_4.
Molecular Weight: 141.96

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

DMF Number and Type	Item referenced	Holder	Status	Review Date and Reviewer's Name	Letter Date

RELATED DOCUMENTS (if applicable): None

CONSULTS:
Dissolution to Biopharmaceutics (pending)
Nomenclature to OPDRA (pending)
Statistics (pending)

REMARKS/COMMENTS:

- The NDA holder submitted amendment dated 06/01/00 that contains responses to our information request letter dated May 24, 2000. The responses were reviewed and evaluated and found satisfactory.
- The applicant provided amendment dated 06/06/00 which contains stability data for clinical batch no. [redacted] However, these are supporting data and only stability data from validation batches will be used for expiry dating. The firm submitted only [redacted] of real time stability data obtained form validation batches (see amendment dated March 29, 2000, Chemistry Review No.1).
- The Original trade name (Diacol) was found unacceptable by to Office of Post-Marketing Drug Risk Assessment (OPDRA). The NDA holder submitted amendment dated 06/22/00, which contains new alternative trade names (first choice is Visicol and second choice is Vucol). The names have been consulted to OPDRA (HFD-400) for review.
- Establishment Inspection (EES) report dated (06/20/00) indicated that 3 sites were inspected and found acceptable. [redacted]

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable form the Chemistry, Manufacturing and Controls point of view. Before this application can be approved, the following conditions should be met:

- Additional real time stability data from the validation batches is needed to determine the expiry dating of the drug product. The firm submitted only [redacted] of real time stability data from the validation batches.

[redacted]

/S/ 07/03/00
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 7/3/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA # 21-970
HFD-180/L.Talarico
HFD-180/Div File/NDA # 21-970
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
HFD-181/A.Kucuba
HFD-820/J.Gibbs
R/D Init by:

SEP - 7 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-097 **CHEMEMISTRY REVIEW #:** 3 **REVIEW DATE:** 09/05/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (BZ)	07/03/00	07/05/00	07/13/00
Amendment (BZ)	07/25/00	07/26/00	08/08/00
Amendment (BZ)	08/07/00	08/08/00	08/08/00
Amendment (BZ)	08/22/00	08/25/00	08/30/00
Amendment (BZ)	08/31/00	09/01/00	09/05/00

NAME & ADDRESS OF APPLICANT:
InKine Pharmaceutical Company, Inc.
Sentry Park East
1720 Walton Road
Blue Bell, Pennsylvania 19422

DRUG PRODUCT NAME:

Proprietary:	Visicol™
Nonproprietary/USAN:	Sodium Phosphate Monobasic (USP) Sodium Phosphate Dibasic Anhydrous (USP)
Code Name/#:	INKP-100
Chem.Type/Ther.Class:	7/S

PHARMACOLOGICAL CATEGORY: Purgative

INDICATION: Cleansing of the bowel when required as a preparation for certain diagnosis procedure, such as colonosocopy, in adults 18 years of age or older.

DOSAGE FORM: Solid Oral Dosage

STRENGTH: 2.0 mg tablets

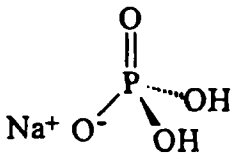
ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx √ OTC ___

SPECIAL PRODUCT: Yes √ No ___

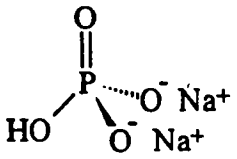
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Sodium Phosphate Monobasic (USP)



Molecular Formula: $NaH_2PO_4.H_2O$
Molecular Weight: 137.99

Sodium Phosphate Dibasic Anhydrous (USP)



Molecular Formula: Na_2HPO_4.
Molecular Weight: 141.96

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL.

SUPPORTING DOCUMENTS:

DMF Number and Type	Item referenced	Holder	Status	Review Date and Reviewer's Name	Letter Date

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Biopharmaceutics

Review completed and dated August 18, 2000. However, additional dissolution data regarding [redacted] was requested from the applicant.

Nomenclature to OPDRA

Review completed and dated August 08, 2000. The new trade name, Visicol, for the drug product is acceptable.

Statistics

Review completed and dated August 10, 2000.

REMARKS/COMMENTS:

- Amendment dated July 03, 2000. This amendment contains 24 months satisfactory stability data [redacted] for clinical batches numbers [redacted]
- Amendment dated July 25, 2000. This document contains up to 6 months of satisfactory stability real time data for 3 validation batches generated at [redacted] The firm has previously submitted stability data for [redacted] time periods for these batches.
- Amendment dated August 07, 2000. This amendment contains responses regarding pH of Visicol tablets and additional dissolution information.
- Amendment dated August 22, 2000. This amendment contains revised patent information and certification.
- Amendment dated August 31, 2000. This document contains the revised chemistry labeling issues. The firm incorporated the following changes:
  - The Chemical Structures included in the label insert
  - The amount of the active ingredients in each tablet specified in "How Supplied" section.
  - The name and the address of the manufacturer is be provided
  - The statement "Store in the sealed container at room temperature 77° F (25°C)" is deleted from the storage statement.
- Methods validation packages have been received and were sent to the FDA laboratories for validation.
- Establishment Inspection Report (EER) dated July 07, 2000, indicated all the four sites that are involved in manufacturing, packaging and control of the drug product are acceptable (see attachment).

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The application may be approved form the Chemistry, Manufacturing and Controls point of view. Based on the available stability data obtained form the 3 validation batches (6 months) and the 2 clinical batches (24 months), the firm will be granted an expiration dating of 12 months at [redacted] for the drug product.

/S/ 09/05/00

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 9/7/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

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NDA # 21-970
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