CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-097			
Submission(s):	Type:	Suppl.:	Letter Date:	Date Received:
	7S	00	11/22/99	11/23/99
		BZ	8/7/00	8/8/00
Reviewer:	Sandip K. Roy, Ph.D.			
Team Leader:	Suresh Doddapaneni, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Monobasic sodium phosphate, USP Dibasic sodium phosphate, USP			
Other Name(s):	INKP-100			
Trade Name:	Diacol™ Tablets			
Molecular Weight:	137.99 141.96			
Molecular Formula:	$NaH_2PO_4.H_2O$ Na_2HPO_4			
Relevant IND(s)/NDA(s):				
Drug Class:	Purgative			
Dosage Form:	Immediate Release Tablets (Each 2.0 g tablet contain 1.5 g sodium phosphate)			
Route of Administration:	Oral			
Dosing Regimen:	Usual adult dosage is 40 tablets (60 g); Evening before colonoscopy: 3 tablets every 15 min for a total of 20 tablets. The last dose will be 2 tablets. Day of the colonoscopy: 3 tablets every 15 min for a total of 20 tablets (starting 3-5 hrs before the procedure). The last dose will be 2 tablets.			
Sponsor:	InKline Pharmaceutical Company, Inc.			
Proposed Indication:	Cleansing of the bowel when required as a preparation for certain diagnostic procedures, such as colonoscopy in adults 18 years of age or older			

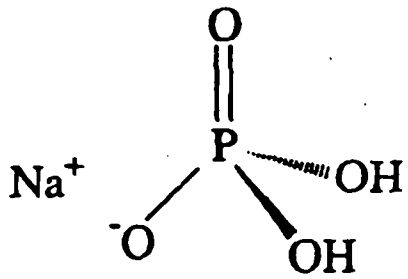
SYNOPSIS

Background

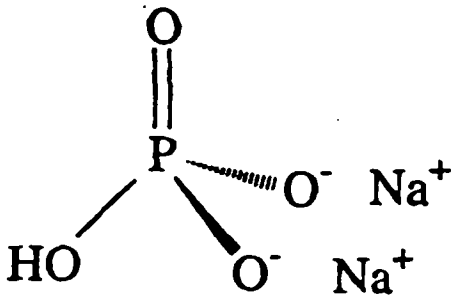
Diacol is a tablet formulation of sodium phosphate with the following active ingredients: 1.102 g sodium phosphate monobasic monohydrate, USP and 0.398 g sodium phosphate dibasic anhydrous, USP. A chemically similar aqueous formulation of sodium phosphate is commercially available at the over-the-counter (OTC) market (Fleet Phospho-Soda). Diacol tablets are a saline purgative whose action is to form a hypertonic salt solution in the bowel, drawing water into the bowel to cause bowel evacuation and cleansing. According to the sponsor, Fleet Phospho-Soda has an unpleasant taste, and causes reactive vomiting in some patients. Diacol tablets were developed in response to patients' requests for a more readily acceptable and palatable purgative preparation.

The structural formulae for Diacol are as follows:

Monobasic sodium phosphate monohydrate, USP



Dibasic sodium phosphate anhydrous, USP



Question Based Review

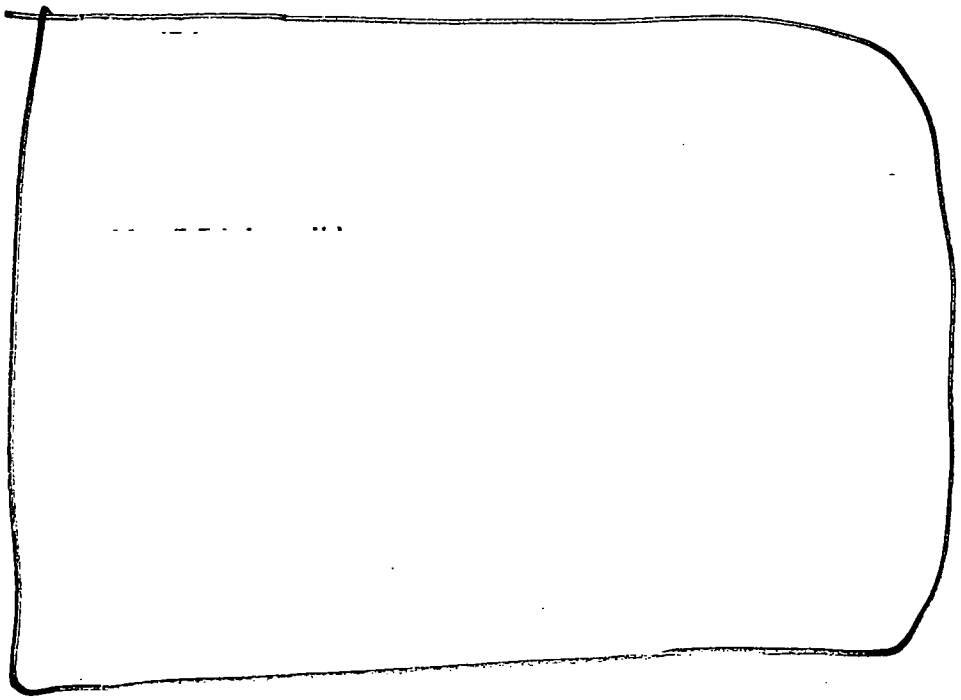
Is the analytical method specific, sensitive, reproducible, and validated appropriately?

What pharmacokinetic information was provided for Diacol?

The pharmacokinetics of serum inorganic phosphorus after oral administration of Diacol was studied in an open-label, single center study in 23 healthy volunteers. Subjects received proposed dosage regimen of 2 oral 30 g doses of Diacol administered 12 hrs apart. Blood samples were collected through 72 hrs after dosing. The mean baseline phosphorus level was approximately 4 mg/dL. Following oral administration of first 30 g dose of Diacol, serum inorganic phosphorus levels increased rapidly to a peak value of approximately 7 mg/dL (3.7 mg/dL above baseline) at a median of 3 hours after dosing. Serum phosphorus levels declined to a mean level of approximately 5 mg/dL at 12 hours after the initial dose. The mean serum phosphorus concentration rose to approximately 8 mg/dL (4.4 mg/dL above baseline) in

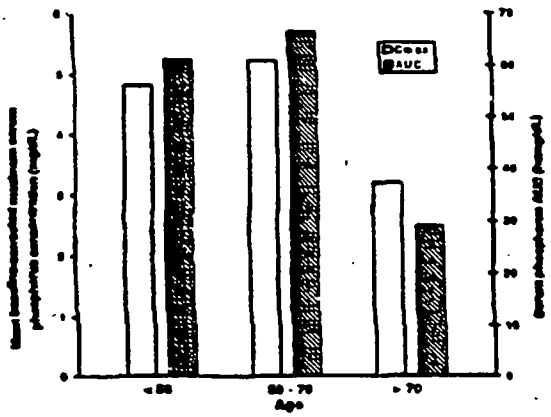
4 hours after the second dose of Diacol. The mean serum level declined to less than 6 mg/dL at 6 hours after the second dose and was within the normal range (2.6 – 4.5 mg/dL) 12 hours after the second dose. The inorganic phosphorus levels returned to baseline values at a median time of 24 hours after the start of the initial dosing.

Absolute serum phosphorus concentrations over time in all subjects

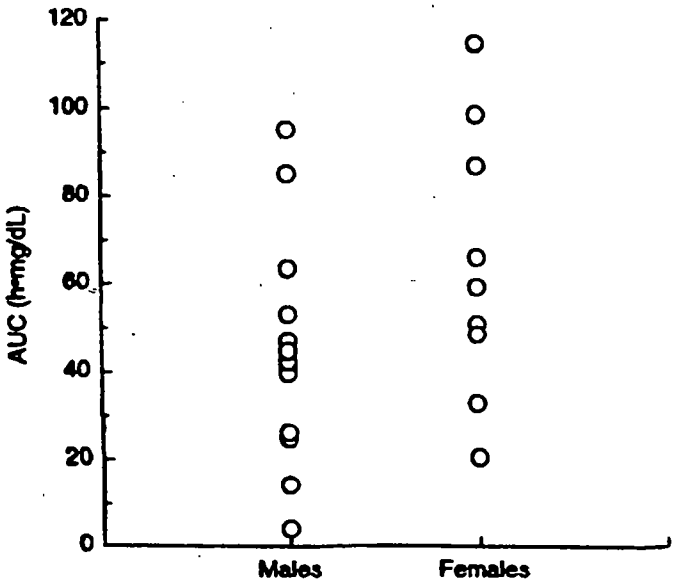


Parameters	PM Dose	AM Dose	Overall
C_{max} (mg/dL)	3.74 ± 1.63	4.40 ± 1.86	4.59 ± 1.75
T_{max} (h)	3.0	4.0	
AUC (h.mg/dL)			55.4 ± 31.1
$T_{1/2}$ (h)			5.50 ± 3.52

Both AUC and C_{max} were reduced by >50% in subjects >70 yrs of age. Based on these results 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).



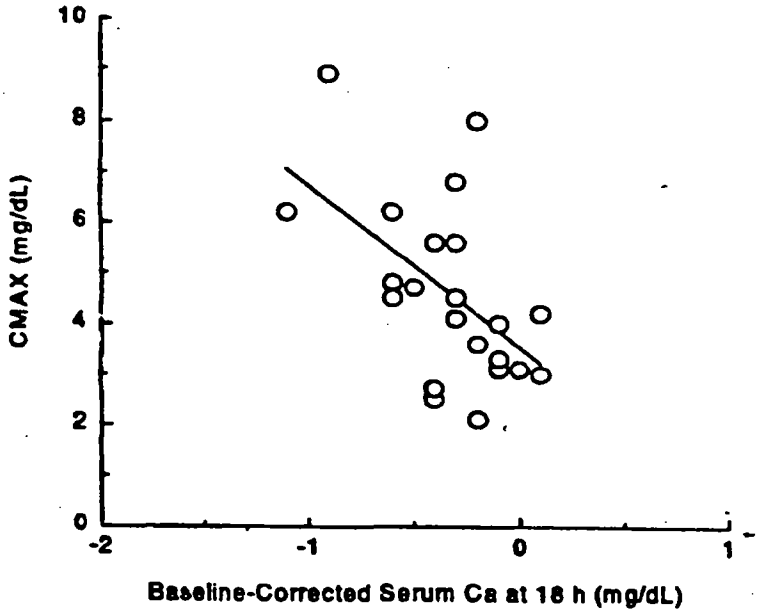
No difference in serum phosphate AUC values were observed between genders in the single pharmacokinetic study conducted in 13 male and 10 female healthy volunteers.



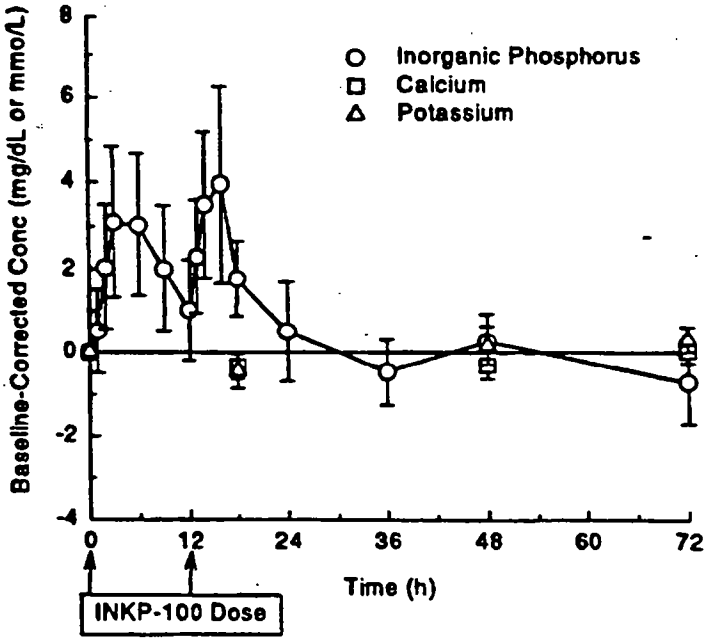
What relationship exists between plasma drug concentrations and adverse effects, if any?

Data from multiple clinical trials have shown that Diacol is associated with transient electrolyte changes. The changes include increase in serum sodium and phosphorus levels, and decreases in serum calcium and potassium levels. It is believed that QTc prolongation observed in few patients in these trials are secondary to changes in serum potassium and calcium.

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.



Hypophosphatemia (≤2.0 mg/dL) at 72 hr occurred in one subject in the > 70 yrs age group and hyperphosphatemia (≥8.6 mg/dL) occurred in 5 subjects in 50-70 yrs group and 3 subjects in the < 50 yrs group. No hypercalcemia (>12 mg/dL) or hypocalcemia (<7 mg/dL) occurred in this study.

What studies/analyses were conducted in order to determine if dose adjustment is required based on intrinsic and extrinsic factors (e.g. renal impairment, drug-drug interaction, food effect, gender effect, etc.)?

The ionized, inorganic form of phosphate in the circulating plasma is excreted almost entirely by the kidneys. Diacol is not expected to be metabolized in liver. It is unlikely that Diacol pharmacokinetics will be altered in patients with hepatic insufficiency. Drug-drug interaction and food effect studies are not needed. These studies were not considered important, since Diacol is designed for one time intake under fasting condition for cleansing of the bowel required as a preparation for certain diagnostic procedures.

Since the ionized, inorganic form of phosphate in the circulating plasma is excreted almost entirely by the kidneys, it is important to determine the effect of renal dysfunction on Diacol disposition. Patients with a serum creatinine > 2.0 mg/dL were excluded from all of the InKline trials of Diacol. Patients in the two Phase III trials had creatinine clearances as low as 31 ml/min. All patients were able to substantially clear the ingested phsophate load by 48 to 72 hrs. However, patients with more severe renal disease than this may have difficulty excreting a large phosphate load. Thus, Diacol should be used with caution in patients with renal impairment.

As shown above, AUC and C_{max} values were lower (<50%) in subjects >70 yrs of age. However, the plasma half-life of inorganic phosphorus was longer (2-fold) in these patients compared to subjects <50 yrs age.

In addition, no difference in serum phosphate AUC values were observed between genders based on the study conducted in 13 male and 10 female healthy volunteers.

Does the dissolution test conditions and specifications appear to be appropriate to the physiologic state and related to in vivo conditions for studying bioavailability and bioequivalence?

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

/S/

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

8/17/2000
Date

FT initiated by Suresh Doddapaneni, Ph.D. /S/ 8/18/00

c.c. /NDA 21-097
/HFD-180 (Division files, AKacuba)
/HFD-870 (SDoddapaneni, SHuang, SRoy)
/CDR (ZZadeng)
HFD-180/A. Al-Hakim
HFD-180/L. Zhou
HFD-180/R. Privant
HFD-180/H. Gallo-Torres
HFD-180/S. Aurocchia