CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

PHARMACOLOGY REVIEW

NDA 21, 097

MAR 21 2000

SPONSOR & ADDRESS: InKine Pharmaceutical Company, Inc.
Blue Bell, Pennsylvania.

REVIEWER: Tamal K. Chakraborti, Ph.D.
Pharmacologist

DATE OF SUBMISSION: November 22, 1999

DATE OF HFD-180 RECEIPT: November 24, 1999

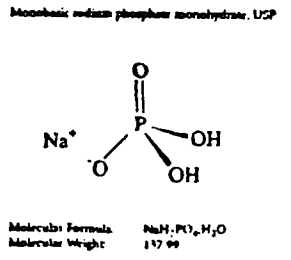
DATE OF REVIEW: March 20, 2000

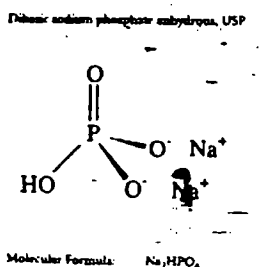
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Summary

DRUG: Diacol™ (INKP-100, Sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) 2.0 g Solid Oral Tablets.

CHEMICAL NAME AND STRUCTURE: Phosphoric acid, monosodium salt, monohydrate; Phosphoric acid, disodium salt, anhydrous.





MOLECULAR FORMULA: $NaH_2PO_4.H_2O/Na_2HPO_4$

MOLECULAR WEIGHT: 137.99/141.96

FORMULATION: Each 2 g Diacol tablet contains the following:

Active Ingredients (1.5 g of active sodium phosphate)

Sodium Phosphate Monobasic Monohydrate, USP 1102.0 mg

Sodium Phosphate Dibasic Anhydrous, USP 398.0 mg

Inactive Ingredients (0.5 g of excipients)

[redacted] Cellulose, NF

Colloidal Silicone Dioxide, NF

Magnesium Stearate, NF

CATEGORY: Bowel cleansing agent.

RELATED DRUGS/INDS/NDAs/MFs:

[redacted] (INKP-100, InKine Pharmaceutical Company, Inc.).
(2) Fleet® Phospho-Soda (C. B. Fleet Co., Inc.).
(3) Fleet® Enema (C. B. Fleet Co., Inc.).

MARKETING INDICATION: Diacol is indicated for cleansing of the bowel in case of preparation of certain diagnostic procedure such as colonoscopy, in adults 18 years of age or older.

DOSE: The usual adult dosage of Diacol for colon cleansing is 40 tablets (60 g of active ingredient) taken in the following manner:

> The evening before the colonoscopy, 3 Diacol tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The last dose is 2 tablets. On the day of the colonoscopy procedure (starting 3-5 h before the procedure), 3 Diacol tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The last dose is 2 tablets.

PRECLINICAL STUDIES AND TESTING LABORATORIES: No preclinical pharmacology/toxicology, absorption, distribution, metabolism, and excretion studies were submitted.

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

SUMMARY AND EVALUATION:

Diacol contains sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP and acts as a saline purgative. The purgative action is mediated through formation of hypertonic salt solution in the bowel, drawing water into the bowel to cause bowel evacuation and cleansing. Colonoscopic examination of the bowel mucosa requires adequate preparative cleansing of the bowel, to remove all normal contents. Currently available ethical preparations consist of various salt solutions and polyethylene glycol (PEG) reconstituted at the time of use and these require patients to swallow 4 liters of solution. One alternative preparation for bowel cleansing is an over-the-counter (OTC) solution of sodium phosphate salts (Fleet® Phospho®-Soda). This preparation has an unpleasant taste and cause reactive vomiting in some patients. However, Fleet® Phospho®-Soda has been in use for decades with a relatively strong safety record.

The sponsor has developed Diacol as oral tablet formulation. The amount (weight in milligrams) of the two sodium phosphate salts (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) was selected to mimic the marketed solution. The sponsor claims that this preparation would be more acceptable and palatable purgative preparation compared to other existing products and would have better patient compliance.

The sponsor in the present New Drug Application proposed to use Diacol for cleansing of the bowel in case of preparation of certain diagnostic procedure such as colonoscopy in adults 18 years of age or older. The usual adult dosage of Diacol for colon cleansing is 40 tablets (60 g of active ingredient) taken in the following manner: The evening before the colonoscopy, 3 Diacol tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The last dose is 2 tablets. On the day of the colonoscopy procedure (starting 3-5 h before the procedure), 3 Diacol tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The last dose is 2 tablets.

In support of the application, the sponsor submitted available literature reports regarding pharmacology of sodium phosphates and their absorption, distribution, metabolism, and excretion in humans. The sponsor did not submit any preclinical pharmacology/toxicology studies in support of this application. There are no toxicology reports available regarding the preclinical oral toxicity data on dibasic sodium phosphate/monobasic sodium phosphate combinations. However, there are some published animal data on the individual phosphates, with limited relevance to the safety of Diacol.

Smyth et al. (Range-finding toxicity data: List VII. *Am Ind Hyg Assoc J* 1969; 30: 470-476) estimated an acute oral LD-50 of dibasic sodium phosphate (administered as 20% w/v in water) in rats as 19.93 g/kg in terms of the heptahydrate. Male beagle dogs were administered by oral gavage with dibasic sodium phosphate at 0.8-1.6 g/kg/day for 22 weeks (Schneider P, Ober KM, and Ueberberg H. Contribution to the phosphate-induced nephropathy in the dog. Comparative light and electron microscopic investigations on the proximal tubule after oral application of K_2HPO_4, Na_2HPO_4, KCL and Nacl. *Exp Pathol* 1981; 19: 53-65). The dogs were sacrificed at 9 and 22 weeks time point and kidneys were examined by light and electron microscopy.

Nephrocalcinosis with disseminated atrophy of the proximal tubule was observed in those animals treated with K_2HPO_4 or Na_2HPO_4.

The tumor promoting effects of phosphates were investigated by Shibata M-A et al. (Comparative promoting activities of phosphate salts on rat two-stage bladder carcinogenesis under conditions of equivalent urinary Na^+ or K^+ levels. *Teratogen Carcinogen Mutagen* 1991; 11: 305-316). Male 344 rats were administered with 2% monobasic sodium phosphate through diet for 32 weeks following initiation with N-butyl-N-(4-hydroxybutyl) nitrosamine, an inducer of bladder carcinogenesis. Monobasic sodium phosphate demonstrated no evidence of tumor promoting activity unlike tribasic sodium phosphate, which promoted tumor activity.

This submission contains published reports regarding absorption, distribution, metabolism and excretion of phosphates in humans and some published literature reports regarding animal toxicology of individual phosphate as mentioned above. There is a lack of published animal toxicity studies in the existing literature on mono and dibasic sodium phosphate combination to support the safety and efficacy of Diacol. However, OTC oral solution of sodium phosphate salts has been in use for decades with a relatively strong safety record. According to 21 CFR Part 201 (May 11, 1998), 16.2 g of dibasic sodium phosphate and 43.2 g of monobasic sodium phosphate may be consumed over an 11-hour period, which is equivalent to the proposed doses of dibasic sodium phosphate (15.92 g) and monobasic sodium phosphate (44.08 g) in Diacol for cleansing of the bowel for colonoscopy. Besides these, several recent clinical trials (Gremse DA et al., *J Pediatr Gastroenterol Nutr* 1996; 23: 586-590; Frommer D, *Dis Colon Rectum* 1997; 40: 100-104; Vecchioli SA et al., *Radiol Med* 1999; 97: 354-359; Oliveira L, *Dis Colon Rectum* 1997; 40: 585-91; Gueller R et al., *Schweiz Med Wochenschr* 1996; 126: 1352-1357; Afridi SA, et al., *Gastrointest Endosc* 1995; 41: 485-489; Huynh T et al., *Am J Gastroenterol* 1995; 90: 104-107; Cohen SM et al., *Dis Colon Rectum* 1994; 37: 689-696; Marshall JB et al., *Aliment Pharmacol Ther* 1993; 7: 679-682) have been conducted with 90 ml/day of oral sodium phosphate solutions (Fleet phospho soda) for bowel preparation for colonoscopy. In all these above-mentioned studies, sodium phosphate solution at this dose level (90 ml/day) was found to be well tolerated and safe. Therefore, the proposed dose of Diacol for cleansing the bowel for colonoscopy appeared to be acceptable.

The labeling of Diacol conforms to the format specified under CFR 21, Subpart B, 201.50-201.57 dated April 1998. However, the suggested changes described in the text, should be incorporated.

RECOMMENDATIONS:

1. From a preclinical standpoint, this NDA may be approved.

2. Sponsor should be asked to change the proposed label of Diacol as suggested in the text of the review.

/S/ 3/20/00

Tamal K. Chakraborti, Ph.D. Date
Pharmacologist

Comment: None

/S/ 3/21/00

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Pharmacology Team Leader

cc:
Original NDA 21-077
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary
HFD-345/Dr. Viswanathan

R/D Init.: J. Choudary 2/29/00

TC/ deg: 3/20/00