

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-892**

**PHARMACOLOGY REVIEW**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-892  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: April 29, 2005  
PRODUCT: —™ (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)  
INTENDED CLINICAL POPULATION: Adult patients undergoing colonoscopy  
SPONSOR: Salix Pharmaceuticals, Inc.  
DOCUMENTS REVIEWED: EDR/NDA 21-892  
REVIEW DIVISION: Division of Gastroenterology Products (HFD-180)  
PHARM/TOX REVIEWER: Tamal K. Chakraborti, Ph.D.  
PHARM/TOX SUPERVISOR: Jasti B. Choudary, B.V.Sc., Ph.D.  
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PROJECT MANAGER: Tanya Clayton, B.S.

Date of review submission to Division File System (DFS):

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## EXECUTIVE SUMMARY

### I. Recommendations

InKine Pharmaceutical Company, Inc (InKine) submitted this New Drug Application (NDA) for            (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.            is a reformulation of Visicol<sup>®</sup> Tablets (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP (approved under NDA 21-097 on September 21, 2000). Soon after the commercial launch of Visicol (INKP-100), the sponsor received reports of a whitish flocculent residue of microcrystalline cellulose (MCC), predominantly in the cecum and ascending colon that, in some cases, obscured mucosal visualization during colonoscopy and was time consuming to remove. In order to overcome this problem, the sponsor has developed this new formulation. The most important compositional change in INKP-102 is that the insoluble binder in Visicol, MCC, has been replaced with polyethylene glycol 8000 (PEG 8000), a water-soluble binder, in order to minimize the use of water-insoluble ingredients in the formulation which might interfere with the visualization procedure during colonoscopy.

- A. Recommendation on approvability: From a preclinical standpoint, this NDA may be approved.
- B. Recommendation for nonclinical studies: None
- C. Recommendations on labeling: The sponsor may be asked to modify the proposed label of            as suggested in the text of this review.

### II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings:            (INKP-102) is a new formulation of Visicol<sup>®</sup> Tablets (sodium phosphate monohydrate, USP, and sodium phosphate dibasic anhydrous, USP) already approved under NDA 21-097 with the same active ingredients in the same amounts. In the new            formulation, the microcrystalline cellulose has been replaced with PEG 8000 in order to minimize the use of water-insoluble ingredients in the formulation which might interfere with the visualization procedure during colonoscopy. The sponsor submitted a report of an *in vitro* osmolarity study to examine the contribution of PEG 8000 to the osmotic activity of the INKP-102 formulation. The sponsor has referred and authorized the Agency to refer to NDA 21-097 for the nonclinical information.
- B. Pharmacologic activity: In addition to information from the Visicol (NDA 21-097), the sponsor has conducted one *in vitro* study examining the

contribution of the PEG 8000 content of INKP-102 to the osmotic activity of the INKP-102 formulation (Study TRD- 00064). The results of this study indicated that the contribution of PEG-8000 to the osmotic activity of INKP-102 was negligible.

C. Nonclinical safety issues relevant to clinical use: None.

**APPEARS THIS WAY  
ON ORIGINAL**

**Relevant INDs/NDAs:**

IND 56,291 (INKP-100, Inkin Pharmaceutical Company, Inc., HFD-180)  
 NDA 21-097 (INKP-100, Salix Pharms, HFD-180)

**Drug Class:** Bowel cleansing agent

**Intended Clinical Population:** Adult patients undergoing colonoscopy

**Clinical Formulation:** INKP-102 Tablets contain the following ingredients:

**Active Ingredients:** Sodium Phosphate Monobasic Monohydrate, USP Sodium Phosphate Dibasic Anhydrous, USP

**Inactive Ingredients:** Polyethylene Glycol 8000, NF and Magnesium Stearate, NF

The quantitative composition of — (New) and Visicol (old) tablets is shown in the following table (from page 1 of pharmacology review of NDA 21-097 dated April 27, 2004).

	Current Formulation, mg	New Formulation, mg
Sodium phosphate monobasic monohydrate, USP	1102	1102
Sodium phosphate dibasic anhydrous, USP	398	398
_____	_____	_____
Magnesium stearate, NF	_____	_____
_____	_____	_____
_____	_____	_____
Total	_____	_____

**Route of Administration:** Oral

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**For 505(b)(2) applications:**

**Data Reliance:** All data and information discussed below and necessary for approval of NDA 21-892 are owned by Inkin Pharmaceutical Company.

**Studies Reviewed Within this Submission:** *In vitro* study examining the contribution of the PEG 8000 content of INKP-102 to the osmotic activity of the INKP-102 formulation (Study TRD- 00064).

**Studies Not Reviewed Within This Submission:** None

**2.6.2 PHARMACOLOGY**

Osmolarity Determinations for \_\_\_\_\_ (TRD-00064)

The primary goal of this study was to determine the contribution of PEG 8000 to the osmolarity of INKP-102 as a tablet binder. In this study, osmolarity determinations were made on six aqueous solutions constituted from \_\_\_\_\_

\_\_\_\_\_ The summary of the data is provided below (from page 4 of the study report).

Sample #	Description	Osmolarity (Osm/L)	
		Theoretical	Actual*

The osmolarity of Visicol (0.3285 Osm/l) and INKP-102 (0.3335 Osm/l) appeared to be comparable. Overall, the results of this study indicated that the contribution of PEG-8000 to the osmotic activity of INKP-102 was negligible.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY**

None submitted.

**2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

None submitted

**2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

None submitted.

**2.6.6 TOXICOLOGY**

No preclinical study reports were submitted

**2.6.7 TOXICOLOGY TABULATED SUMMARY**

No preclinical study reports were submitted.

**LABELING**

The draft labeling of \_\_\_\_\_ generally conforms to the format specified under 21CFR, Subpart B-Labeling Requirements for Prescription Drugs. However, the following changes should be incorporated.

**Pregnancy**

**Sponsor's Version:**

**Pregnancy**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Evaluation:** The text is not in accordance with 21CFR 201.57(f)(6)(i)(c). The labeling should be modified as proposed below.

**Proposed Version:**

**Pregnancy. Teratogenic Effects: Pregnancy Category C.**

Animal reproduction studies have not been conducted with \_\_\_\_\_. It is also not known whether \_\_\_\_\_ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. \_\_\_\_\_ should be given to a pregnant woman only if clearly needed.



**Unresolved Toxicology Issues:** None

**Recommendations:** From a preclinical standpoint, NDA 21-892 for \_\_\_\_\_<sup>TM</sup> submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act may be approved.

**Suggested Labeling:** The sponsor may be asked to change the proposed label of \_\_\_\_\_<sup>TM</sup> as suggested in the text of the review.

Signatures (optional):

Reviewer Signature \_\_\_\_\_

Supervisor Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

cc:

- Original NDA
- HFD-180
- HFD-181/CSO
- HFD-180/Dr. Chakraborti
- HFD-180/Dr. Choudary
- HFD-048/Dr. Viswanathan

R/D Init. J Choudary: 1/31/06

**APPENDIX/ATTACHMENTS**

None

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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