CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-892

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-892

Letter Date: 4/29/05

Proposed Brand Name: [redacted]

Generic Name: Sodium phosphate

Reviewers: Suliman I. Al-Fayoumi, Ph.D.

Team Leader: Dennis Bashaw, Pharm.D.

OCPB Division: Clinical Pharmacology Evaluation 3

Sponsor: Salix Pharmaceuticals

Submission Type: Original NDA (3 S)

Formulation, Strength(s): Immediate-Release Tablet, 1.5 g

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

Proposed Dosage Regimen: The usual adult dosage of [redacted] Tablets for colon cleansing is 32 tablets taken orally in the following manner:
The evening before the colonoscopy procedure, take 4 [redacted] Tablets with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The day of the colonoscopy procedure, (starting 3-5 hours before the procedure) take 4 [redacted] Tablets with 8 ounces of clear liquids every 15 minutes for a total of 12 tablets.

Executive Summary

[redacted] Tablets are a saline purgative that acts by forming a hypertonic salt solution in the bowel, which draws water into the bowel to cause bowel evacuation and cleansing.

[redacted] (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets contain 1.5 g of active sodium phosphate salts and [redacted] g of excipients. [redacted] is a reformulation of Visicol® Tablets (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP [NDA 21-097, approved September 21, 2000]). Moreover, the proposed indication for [redacted] is the same as for Visicol®.

Compared to Visicol®, [redacted] has identical active ingredients but different excipients. The only significant compositional change in [redacted] is that the insoluble binder in Visicol®, microcrystalline cellulose (MCC), has been replaced with PEG 8000, a highly water-soluble tablet binder. This change was prompted by reports [redacted] (apparently composed of MCC) [redacted] following administration of Visicol® Tablets that at times obscured mucosal visualization during colonoscopies. In addition, the proposed dose of [redacted] (48 g) is lower than the recommended dose of Visicol® (60 g).

Overall, two clinical studies were submitted under this application including a phase 2, dose ranging study (n = 210) and a randomized, multi-center, phase 3 study (n = 675). No clinical pharmacology data were submitted under this application. Given the chemical nature of the active components of ——® (i.e. a hypertonic salt solution) and its mode of action, no in vivo bioavailabilty assessment was undertaken nor will be required per 21CFR320.22(b)(3).

The phase 2, dose-ranging study compared six dosing regimens of —— tablets ranging from 42 to 60 g (28 to 40 tablets) to the approved Visicol®tablets 60 g when administered at evening only or split evening and next day dosing. The best-performing —— tablets regimens (based on response rates) were the higher, split-dose arms: 60g (97%), 60g (100%), and 48g (97%).

In the phase 3 study, two dosing regimens of ——tablets (48 g and 60 g) were compared to the approved Visicol®tablets 60 g. The overall response rate for colonic cleansing was 92.6%, with both the —— tablets 60 g (95.7%) and —— tablets 48 g (93.6%) arms having significantly (P = 0.0272) higher response rates than the Visicol®tablets arm (88.5%).

The clinical trial formulation of —— is identical to the commercial to-be-marketed formulation (i.e., formulation 1219-11). Comparative dissolution data demonstrate that —— tablets are rapidly dissolving with virtually complete dissolution achieved within 15 min (Table 2).

Table 1. Quantitative composition of —— tablets

Material Description	% w/w	Mg per tablet	Quantity per batch (kilos)
Sodium Phosphate Monobasic Monohydrate, USP	——	1102.0	——
Sodium Phosphate Dibasic Anhydrous, USP	——	398.0	——
Polyethylene Glycol 8000, NF	——	——	——
Magnesium Stearate, NF	——	——	——
TOTAL:	——	——	——

Comparative Dissolution Profile – Batch # 1219-11, -12 & Visicol™ Tablets

Batch ID	Average Percent Released (%)					
	15 min	20 min	30 min	45 min	60 min	90 min
Visicol™ (n=6)	N/A	40.35	50.57	65.40	77.72	95.38
1219-11 (n=3)	N/A	98.00	98.77	96.10	96.80	96.00
1219-12 (n=3)	92.23	N/A	95.57	95.23	N/A	N/A

* Formulations 1219-11 and 1219-12 are identical with the exception of the addition of 0.5% magnesium stearate in formulation 1219-11.

1.1 Recommendation

As this product is a reformulation of a previously approved product, with a new binding agent, no in vivo bioavailability trials were submitted in this NDA. It is the opinion of the Office of Clinical Pharmacology that this application meets the *in vivo* bioavailabilty waiver provisions of 21CFR320.22 (b)(3).

APPEARS THIS WAY
ON ORIGINAL

13 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Appendix 2

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-892	Proposed Brand Name	[redacted]
OCPB Division	3	Generic Name	Sodium phosphate
Medical Division	Gastroenterology	Drug Class	Purgative
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Bowel cleansing
OCPB Team Leader	Dennis Bashaw	Dosage Form	IR tablet
		Dosing Regimen	48 g
Date of Submission	4/29/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	1/29/06	Sponsor	InKine
PDUFA Due Date	2/29/06	Priority Classification	Standard
Estimated Division Due Date	1/29/06		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	Not needed at this time	
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suliman Alfayoumi
2/13/2006 09:53:25 AM
BIOPHARMACEUTICS

Dennis Bashaw
2/13/2006 03:18:17 PM
BIOPHARMACEUTICS