CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-892

CHEMISTRY REVIEW(S)

NDA 21-892

OsmoPrep™

Sodium Phosphate Monobasic (USP)
Sodium Phosphate Dibasic Anhydrous (USP)

Salix Pharmaceuticals, Inc.

Ali Al-Hakim, Ph.D.,
Office of New Drug Quality Assessment
Division of Pre-marketing and Manufacturing Sciences
(Branch V)

Division of Gastroenterology Drug Product (HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA _____

2. REVIEW #: 1

3. REVIEW DATE: March 2, 2006

4. REVIEWER: Ali Al-Hakim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	April 14, 2005
Amendment	May 10, 2005
Amendment	June 22, 2005
Amendment	December 12, 2005

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name:	**NAME & ADDRESS OF APPLICANT:** Salix Pharmaceutical Company, Inc.
Address	Sentry Park East 1720 Walton Road Blue Bell, Pennsylvania 19422
Representative:	Michael Angioli, Director of regulatory affairs
Telephone:	302 885-1389

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	OSMOPREP
b) Non-Proprietary Name (USAN):	Sodium Phosphate Monobasic (USP) Sodium Phosphate Dibasic Anhydrous (USP)
c) Code Name #	INKP-100
d) Chem. Type/Submission Priority	Standard
• Chem. Type:	5
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

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

11. DOSAGE FORM: Tablet (oral solid)

12. STRENGTH/POTENCY: 1.5 g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: √ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

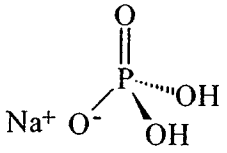
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Approved name(s) **OsmoPrep**

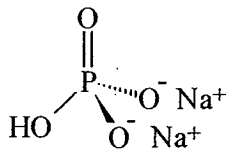
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF Number and Type	Item referenced	Holder	Status	Review Date and Reviewer's Name	Letter Date
Type II			Adequate[3]	04/07/2000 Ali Al-Hakim	
Type II			Adequate[3]	04/07/2000 Ali Al-Hakim	
Type III			Adeqauet[4]	4/11/1995 James Vidra HFD-540	
Type III			Adequate[3]	12/05/1999 Susan Rosencrance, HFD-643	
Type III			Adequate[3]	04/13/2000 Ali Al-Hakim	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21097 (Visicol)	This is the original NDA application which formulated with the microcrystalline cellulose

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable		
EES	Acceptable	June 17, 2005	D Ambrogio, Janine M
Pharm/Tox	Acceptable		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Acceptable	December 23, 2005	Ali Al-Hakim
DEMTS	Acceptable	February 22, 2006	
EA	Acceptable	May 30, 2004	Ali Al-Hakim
Microbiology	N/A		

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-689

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The NDA is recommended for approval from CMC standpoint of view (see bases for approvability in section C below).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance,
The drug substance section of the NDA is located in DMF____ (sodium phosphate monobasic, USP) and DMF ____ (sodium phosphate dibasic, USP). These DMF were reviewed and found acceptable. Therefore, for information regarding the drug substance, see the reviews of the above two DMFs.

Note
All required CMC information regarding the two APIs in the formulation of INKP-102 tablets can be found in the CMC section of NDA 21-097, Salix's approved NDA for Visicol® Tablets.

As part of the End of Phase 2 meeting for INKP-102, Salix requested that, since the two APIs of INKP-102 (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) are the same APIs being used in the current formulation of Visicol®, and the information that would be required in the new NDA is exactly the same as what has already been submitted in Salix's approved NDA 21-097 for Visicol®, Salix intends to simply reference the Visicol® NDA for information relating to the APIs in its planned NDA for INKP-102. The agency agreed that the sponsor can refer to the NDA for the API, but not for the formulation. Please see the FDA's minutes (dated August 31, 2004) of our August 23, 2004 End of Phase 2.

The drug product
OsmoPrep (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP) is a purgative used to clean the colon prior to colonoscopy. OsmoPrep is manufactured with a highly soluble tablet binder and does not contain microcrystalline cellulose (MCC). OsmoPrep tablets are white to off-white compressed tablets. Each tablet contains 1.102 g of sodium phosphate monobasic monohydrate,

- The usual adult dosage for colon cleansing is 32 tablet taken orally. The patient should take, evening before the colonoscopy procedure, 4 OsmoPrep 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), additional 4 OsmoPrep tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 12 tablets.

C. Basis for Approvability or Not-Approval Recommendation

The NDA is recommended for approval from CMC point of view because of the following points:

Regarding the drug substances:

- The applicant provided the essential CMC information for the drug substance by referencing NDA 21-097 (Visicol) which was approved in 2001. Additional information regarding specifications, tests, certificate of analysis, etc, were also provided in the NDA.

With respect to the drug product:

- Although the only difference between the approved NDA and the current one is that the formulation (replacing microcrystalline cellulose with polyethylene glycol 8000 and the amount of [redacted] was [redacted] however, the NDA applicant provided complete CMC section for the drug product which included:
- Manufacturing process
  - A comprehensive pharmaceutical development/validation report describing the formulation/manufacturing science and development details which led to the development of the new formulation.
  - Process controls ([redacted])
  - Acceptance criteria (test methods and limits)
  - Test data from pre-clinical, clinical and NDA validation batches
  - Satisfactory stability data, packaging and labeling

The above information were reviewed and assessed regarding the adequacy of the manufacturing science and its impact on the drug product quality and the ability of the applicant to produce consistent batches that meet the proposed specifications throughout the IND development program (pre-clinical and clinical batches) leading to the NDA validation batches.

III. Administrative

A. Reviewer's Signature
Ali Al-Hakim, Ph.D.

Branch Chief's Signature
Moo-Jhong Rhee, Ph.D.

B. Endorsement Block

CC:
HFD-180/NDA 21-892
HFD-180/Division of Gastroenterology/B. Harvey
Division of Gastroenterology/T. Clayton
DPMAS/ONDQA/A. Al-Hakim
DPMAII/ONDQA/M.J. Rhee
03/01/2005 Wordfiles/NDA 21892

37 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Ali Al-Hakim
3/14/2006 04:11:18 PM
CHEMIST

Moo-Jhong Rhee
3/14/2006 04:26:49 PM
CHEMIST
Chief, Branch III