DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-097
NDA 21-892

Salix Pharmaceuticals, Inc.
Attention: Gail Glifort, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your new drug application NDA 21-097 for Visicol (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets which was approved on September 21, 2000, and your NDA 21-892 for OsmoPrep (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets, which was approved on March 26, 2006.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require sponsors of approved drugs to conduct postmarketing studies and clinical trials (section 505(o)(3) of the FDCA), develop and comply with Risk Evaluation and Mitigation Strategies (REMS) (section 505-1 of the FDCA) and make safety related labeling changes (section 505(o)(4) of the FDCA) based upon new safety information that becomes available after approval of the drug. These provisions took effect on March 25, 2008.

In March 2006, information regarding the risks of acute phosphate nephropathy (a type of acute kidney injury) associated with the use of oral sodium phosphate products for bowel cleansing was added to the Warnings section of the existing labeling for Visicol and incorporated into the labeling with which OsmoPrep was approved on March 16, 2006. In May 2006, an FDA Alert and science background paper were posted for healthcare professionals detailing cases of acute phosphate nephropathy associated with the use of oral sodium phosphate products for bowel cleansing.

Since May 2006, FDA has continued to receive reports of acute kidney injury with both prescription and over-the-counter oral sodium phosphate products. Twenty unique cases of acute kidney injury associated with the use of OsmoPrep were reported which included 3 cases of biopsy proven acute phosphate nephropathy. In addition, observational retrospective cohort studies were published which reported an increased risk of acute kidney injury in patients undergoing bowel cleansing using oral sodium phosphate products, as defined by changes in

serum creatinine.[1,2,3,4] We consider this information to be "new safety information" as defined in FDAAA.

After consideration of the new safety information described above, we believe that safety related changes should be included in the labeling for Visicol and OsmoPrep. We have also determined that a REMS for each drug is necessary to ensure that the benefits of the drugs outweigh the risks. Finally, we are requiring you to conduct a postmarketing clinical trial to assess a known serious risk. These requirements are described further below.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, you must make the following safety related changes to the labeling for Visicol and OsmoPrep.

We have concluded that the prescribing information for Visicol and OsmoPrep should be updated as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

- The addition of a B**oxed Warning** to alert prescribing physicians of the risks of acute kidney injury with use of oral sodium phosphate products, to include the following language:

WARNINGS
There have been rare, but serious reports of acute phosphate nephropathy in patients who received oral sodium phosphate products for colon cleansing prior to colonoscopy. Some cases have resulted in permanent impairment of renal function and some patients required long-term dialysis. While some cases have occurred in patients without identifiable risk factors, patients at increased risk of acute phosphate nephropathy may include those with age 55 years and above, hypovolemia, increased bowel transit time (such as bowel obstruction), active colitis, or baseline kidney disease, and those using medicines that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]). *See* **WARNINGS**.

[1] Hurst F, *et al.* Association of oral sodium phosphate purgative use with acute kidney injury. *J Am Soc Nephrol* 18: 3192-3198; 2007.
[2] Brunelli SM, Lewis JD, Gupta M, et al. Risk of kidney injury following oral phosphosoda bowel preparations. *J Am Soc Nephrol* 18: 3199-3205; 2007
[3] Markowitz GS, Radhakrishnan J and D'Agati VD. Towards the incidence of acute phosphate nephropathy. *J Am Soc Nephrol* 18: 3020-3022; 2007
[4] Russmann, S, Lamerato L, Marfatia A, et.al. Risk of impaired renal function after colonoscopy; a cohort study in patients receiving either oral sodium phosphate or polyethylene glycol. *Am J Gastroenterol* 102: 2655-2663, 2007.

MEDICATION GUIDE
In addition to the changes described above to the labeling, you should submit a proposed Medication Guide for Visicol and OsmoPrep. Your Medication Guide must include information about the serious risk of acute kidney injury and will be considered part of the proposed REMS. Pursuant to 21 CFR Part 208 and 505-1(e)(2), FDA has determined that Visicol and OsmoPrep pose a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe use of Visicol and OsmoPrep. FDA has determined that Visicol and OsmoPrep are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Visicol and OsmoPrep. FDA has determined that Visicol and OsmoPrep are products for which patient labeling could help prevent serious adverse events.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling for Visicol and OsmoPrep in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

Use the following designators to prominently label all submissions, including supplements, relating to this safety labeling change as appropriate:

Safety Labeling Changes under 505(o)(4)

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In accordance with section 505-1(a) of the FDCA, we have determined that a REMS is necessary for Visicol and for OsmoPrep to ensure that the benefits of the drugs outweigh the risks based on the new safety information described above.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. The approved Medication Guide submitted as a safety labeling change, noted above, will be considered part of the REMS in accordance with 505-1(a). As described above, pursuant to 21 CFR Part 208 and 505-1(e)(2), FDA has determined that Visicol and OsmoPrep pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe use of Visicol and OsmoPrep. FDA has determined that Visicol and OsmoPrep have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Visicol and OsmoPrep. FDA has determined that Visicol and OsmoPrep are products for which patient labeling could help prevent serious adverse events. Under 21 CFR 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Visicol or OsmoPrep.

Communication Plan: We have determined that a communication plan to gastroenterologists, surgeons, primary care physicians, and other healthcare providers who are likely to prescribe or dispense oral sodium phosphate products including Visicol or OsmoPrep and/or perform follow-up assessments of patients following bowel cleansing, will support implementation of the elements of your REMS. Such a plan may include Dear Healthcare Provider (DHCP) letters, a prescriber brochure with key safety messages, or product website postings. All communication plan materials must be submitted for review.

Timetable for Assessment: The proposed REMS should include a timetable for assessment of the REMS that shall be no less frequent than by 18 months and 3 years after the REMS is approved, and in the 7th year after the REMS is approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the assessment interval.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

In accordance with section 505-1, within 60 days of the date of this letter, you must submit a proposed REMS. The REMS, once approved, will create enforceable obligations.
We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Visicol and OsmoPrep. Additionally, all relevant proposed REMS materials including enrollment forms, informed consents, and educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Visicol and OsmoPrep
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If you do not submit electronically, please send 5 copies of your proposed REMS and REMS Supporting Document as an amendment to NDAs. Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 21-097 and 21-892

PROPOSED REMS

On the first page of subsequent submissions related to your proposed REMS, prominently identify the submission by including this wording in bold, capital letters at the top of the page:

SUPPLEMENT [assigned #]
PROPOSED REMS - AMENDMENT

POSTMARKETING REQUIREMENTS UNDER 505(o)

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of acute kidney injury (including acute phosphate nephropathy) following Visicol or OsmoPrep use.

Furthermore, the new pharmacovigilance system that FDA is required to establish under subsection 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this known serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk in patients who are taking Visicol or OsmoPrep for bowel cleansing and to better define what risk factors may predispose patients to such injury.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial:

1. A prospective, randomized, active-controlled trial comparing the risk of developing acute kidney injury in patients undergoing bowel cleansing using Visicol or OsmoPrep as compared to patients undergoing bowel cleansing using polyethylene glycol (PEG) containing products.

Your protocol for this trial should include an appropriate pre-specified primary outcome to assess acute kidney injury (e.g., increase in baseline creatinine following treatment). Laboratory testing at baseline and at pre-determined intervals following bowel cleansing should be assessed. The overall duration of follow-up should be specified, and your rationale for the adequacy of such follow-up should be submitted with your protocol.

Submit timelines for trial initiation, trial completion, and submission of the final report for the clinical trial described above within 90 days of the date of this letter, and a draft protocol within 180 days.

Submit the protocol to your IND 56,291 with a cross-reference letter to your NDAs 21-097 and 21-892. Submit the final report to your NDAs 21-097 and 21-892. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D.
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Appendix A

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:
A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

Appendix B

REMS Supporting Document Template

The REMS Supporting Document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS and should include the following sections as well as a table of contents:

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use
    c. Implementation System
    d. Timetable for Assessment of the REMS

4. Information Needed for Assessments

5. Other Relevant Information

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

/s/

Joyce Korvick

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