CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-014
NDA 21-892/S-004

Trade Name: Visicol (NDA 21-097/S-014)
OsmoPrep (NDA 21-892/S-004)

Generic Name: sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP

Sponsor: Salix Pharmaceuticals, Inc..

Approval Date: 10/13/2009

Indications: Visicol® Tablets are indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older.

OsmoPrep Tablets are indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older.

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Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-014

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021097/S-014
NDA 021892/S-004

APPROVAL LETTER

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

Dear Mr. Burgin:

Please refer to your supplemental new drug applications dated February 9, 2009, received February 10, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 21-097 for Visicol (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets and NDA 21-892 for OsmoPrep (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets.

We acknowledge receipt of your submissions dated March 6, 2009, July 30, 2009, September 24 2009, and September 30, 2009.

These supplemental new drug applications provide for a proposed Risk Evaluation and Mitigation Strategy (REMS) for Visicol and OsmoPrep as requested in our letter dated December 10, 2008.

We completed our review of these supplemental new drug applications, as amended. They are approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risk of acute phosphate nephropathy associated with the use of oral sodium phosphate products (section 505-1(a)).

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. We considered this information to be "new safety information" as defined in FDAAA.

Your proposed REMS, submitted on February 9, 2009 and amended on July 30, 2009, September 24, 2009, and September 30, 2009 is appended to this letter, and is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

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

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021097 or NDA 021892 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021097 or NDA 021892
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021097 or NDA 021892REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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., M.P.H.
Deputy Director for Safety
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: REMS Documents

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21097	SUPPL-14	SALIX PHARMACEUTICALS INC	VISICOL(SODIUM PHOSPHATE DIBASIC ANHYDRA
NDA-21892	SUPPL-4	SALIX PHARMACEUTICALS INC	OSMOPREP

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

/s/

JOYCE A KORVICK
10/13/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-014
NDA 21-892/S-004

LABELING

IMPORTANT DRUG WARNING

SUBJECT: Boxed Warning for Prescription Oral Sodium Phosphate Products

OsmoPrep® (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)Tablets

Visicol® (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)Tablets

Date: October ____, 2009

Dear Healthcare Professional:

Salix Pharmaceuticals, Inc. would like to inform you of labeling revisions to the OsmoPrep and Visicol U.S. Prescribing Information, to further strengthen and clarify information regarding the risk of acute phosphate nephropathy with the use of these products. A **Boxed Warning** has been added to the prescribing information for OsmoPrep and Visicol as follows:

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 increased age, 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, angiotension converting enzyme [ACE] inhibitors, angiotension receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]). *See* **WARNINGS.**

It is important to use the dose and dosing regimen as recommended (pm/am split dose).

See **DOSAGE and ADMINISTRATION.**

Patients with increased risk of acute phosphate nephropathy include those with

- Increased age
- Hypovolemia
- Increased bowel transit time (such as bowel obstruction)
- Active colitis
- Baseline kidney disease
- Using medicines that affect renal perfusion or function (e.g. diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDS]).

OsmoPrep and Visicol should be used with caution in patients with impaired renal function, patients with a history of acute phosphate nephropathy, severe renal insufficiency (creatinine clearance less than 30 mL/minute), known or suspected electrolyte disturbances (e.g., dehydration). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have their electrolytes corrected before treatment.

OsmoPrep or Visicol should NOT be taken by patients who

- Are taking other laxatives, especially those made with sodium phosphate
- Are allergic to sodium phosphate salts or to any of the ingredients in OsmoPrep or Visicol

Before prescribing OsmoPrep or Visicol, you should be aware of your patient's medical concerns, including a history of

- Seizures
- Electrolyte abnormalities such as a hypocalcemia, hypokalemia, hypernatremia, hyperphosphatemia
- Uncontrolled arrhythmias
- Recent myocardial infarction
- Cardiomyopathy
- Prolonged QT
- Congestive heart failure
- Ascites
- Unstable angina
- Gastric retention
- Ileus
- Any damage to the bowel such as acute bowel obstruction, pseudo-obstruction of the bowel, bowel perforation, acute colitis, or toxic megacolon
- Severe chronic constipation
- Gastric bypass or stapling surgery
- Hypomotility syndrome

Additionally, you should be aware if your patients are taking any of the following therapies and use caution in prescribing OsmoPrep or Visicol:

- Seizure medications or medications that lower the seizure threshold such as tricyclic antidepressants
- Laxatives for constipation (in the last week)
- Low-salt diet

The recommended dose of OsmoPrep for adults is 32 tablets taken 4 at a time. Patients should drink at least 2 quarts of clear liquids with OsmoPrep as follows:

The evening before your colonoscopy: Take 4 OsmoPrep tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 20 tablets.

On the day of the colonoscopy: 3-5 hours before the colonoscopy, take 4 OsmoPrep tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 12 tablets.

The recommended dose of Visicol for adult is 40 tablets. Patients should drink at least 3.6 quarts of clear liquids with Visicol as follows:

The evening before the colonoscopy: Take 3 Visicol tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 20 tablets. (Note: the last dose will only be 2 Visicol tablets.)

On the day of the colonoscopy: 3-5 hours before the colonoscopy, take 3 Visicol tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 20 tablets. (Note: the last dose will only be 2 Visicol tablets.)

It is very important for your patients to drink clear liquids before, during and after the use of OsmoPrep or Visicol because this may help prevent kidney damage. Clear liquids include water, flavored water, lemonade (no pulp), ginger ale, or apple juice. Patients should not drink any purple or red liquids. Instruct patients to tell you if they experience vomiting, dizziness, or decreased urination. This may be a sign that they have lost too much fluid while using OsmoPrep or Visicol. Instruct patients to tell you if they have trouble drinking liquids while taking OsmoPrep or Visicol or experience severe stomach cramping, bloating, nausea, or headache.

In addition to the changes described above to the prescribing information, a Medication Guide has been added for both OsmoPrep and Visicol. The Medication Guide provides patients with important safety information necessary for safe and effective use of OsmoPrep and Visicol. The Medication Guide will be distributed to all patients who are dispensed/administered these products.

Safety information for healthcare professionals regarding OsmoPrep and Visicol may be accessed at www.warninginfoforosmoprepandvisicol.com.

Copies of the revised U.S. Prescribing Information and the Medication Guide for both products are enclosed. The Postmarketing Experience section of the prescribing information has also been updated. We encourage you to review the full prescribing information and discuss the safety information with your patients.

Salix Pharmaceuticals, Inc. is committed to providing you with the most current information to help you in the management of your patients. To report adverse patient experiences or to request further information on Visicol or OsmoPrep, please contact Salix at (800) 508-0024. Alternatively, adverse events may be reported to the FDA's MedWatch reporting system by phone at (800)-FDA-1088, or online at www.fda.gov/medwatch.

Sincerely,

Doug K. Bettenhausen, PharmD
Vice President, Medical Affairs and Product Safety
Salix Pharmaceuticals, Inc.

Salix
PHARMACEUTICALS, INC.

Important Safety Information for OsmoPrep and Visicol

Safe Use of OsmoPrep® and Visicol®

Important information to consider when prescribing sodium phosphate bowel preps from Salix Pharmaceuticals

In response to reports of acute phosphate nephropathy associated with sodium phosphate bowel preps, the FDA required the addition of a boxed warning to the prescribing information for OsmoPrep and Visicol (see below) and the communication of safety information to healthcare professionals. Responsible use of all Salix products has always been a primary objective, so this information has been provided to you to assist in making informed decisions for the health of your patients.

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 increased age, 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 antiinflammatory drugs [NSAIDs]). See **WARNINGS**.

It is important to use the dose and dosing regimen as recommended (PM/AM split dose). See **DOSAGE** and **ADMINISTRATION**.

There are a number of factors you should consider when prescribing OsmoPrep and Visicol. The following information should be used to help your patients safely prepare for a colonoscopy using OsmoPrep or Visicol.

First, about acute phosphate nephropathy

What is acute phosphate nephropathy?

Acute phosphate nephropathy is a form of acute kidney injury that is associated with deposits of calcium phosphate crystals in the renal tubules that may result in permanent renal function impairment. Acute phosphate nephropathy is a rare, serious adverse effect that has been associated with the use of oral sodium phosphate.

What are the warning signs of acute phosphate nephropathy after using an oral sodium phosphate product?

Acute phosphate nephropathy can result in a decrease in kidney function. Symptoms can include malaise, lethargy, drowsiness, oliguria, and peripheral edema. Early stages may not be associated with symptoms and may only be detected by blood tests to measure kidney function (ie, serum creatinine and blood urea nitrogen). It is important to monitor kidney function closely, especially if your patient is at increased risk of developing this side effect.

How soon can kidney problems occur after taking OsmoPrep or Visicol?

Kidney problems may occur within a few days or weeks after taking OsmoPrep or Visicol.

Who is most at risk for developing acute phosphate nephropathy?

Patients with increased risk of acute phosphate nephropathy include those with

- Increased age
- Hypovolemia
- Increased bowel transit time (such as bowel obstruction)
- Active colitis
- Baseline kidney disease
- Using medicines that affect renal perfusion or function (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal antiinflammatory drugs [NSAIDs]).

OsmoPrep and Visicol should be used with caution in patients with impaired renal function, patients with a history of acute phosphate nephropathy, severe renal insufficiency (creatinine clearance less than 30 mL/minute), known or suspected electrolyte disturbances (eg, dehydration). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have their electrolytes corrected before treatment.

While acute phosphate nephropathy is the subject of the boxed warning, there is other safety information that is important to consider when prescribing OsmoPrep or Visicol to your patients.

Who should not take OsmoPrep or Visicol?

OsmoPrep or Visicol should NOT be taken by patients who

- Are taking other laxatives, especially those made with sodium phosphate
- Are allergic to sodium phosphate salts or to any of the ingredients in OsmoPrep or Visicol

What should I know about my patients before prescribing OsmoPrep or Visicol?

Before prescribing OsmoPrep or Visicol, you should be aware of your patient's medical concerns, including a history of

- Seizures
- Electrolyte abnormalities such as hypocalcemia, hypokalemia, hypernatremia, or hyperphosphatemia
- Uncontrolled arrhythmias
- Recent myocardial infarction
- Cardiomyopathy
- Prolonged QT
- Congestive heart failure
- Ascites
- Unstable angina
- Gastric retention
- Ileus
- Any damage to the bowel such as acute bowel obstruction, pseudo-obstruction of the bowel, bowel perforation, acute colitis, or toxic megacolon
- Severe chronic constipation
- Gastric bypass or stapling surgery
- Hypomotility syndrome

Additionally, you should be aware if your patients are taking any of the following therapies and use caution in prescribing OsmoPrep or Visicol:

- Seizure medications or medications that lower the seizure threshold such as tricyclic antidepressants
- Laxatives for constipation (in the last week)
- Low-salt diet

Patients who are pregnant or breastfeeding should only be prescribed OsmoPrep or Visicol if clearly needed.

How should your patients take OsmoPrep?

The recommended dose of OsmoPrep for adults is 32 tablets taken 4 at a time. Patients should drink at least 2 quarts of clear liquids with OsmoPrep as follows:

The evening before the colonoscopy: Take 4 OsmoPrep tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 20 tablets.

On the day of the colonoscopy: 3-5 hours before the colonoscopy, take 4 OsmoPrep tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 12 tablets.

How should your patients take Visicol?

The recommended dose of Visicol for adults is 40 tablets. Patients should drink at least 3.6 quarts of clear liquids with Visicol as follows:

The evening before the colonoscopy: Take 3 Visicol tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 20 tablets. (Note: the last dose will only be 2 Visicol tablets.)

On the day of the colonoscopy: 3-5 hours before the colonoscopy, take 3 Visicol tablets with 8 ounces of **clear liquids** every 15 minutes for a total of 20 tablets. (Note: the last dose will only be 2 Visicol tablets.)

It is very important for your patients to drink clear liquids before, during, and after the use of OsmoPrep or Visicol because this may help prevent kidney damage. Clear liquids include water, flavored water, lemonade (no pulp), ginger ale, or apple juice. Patients should not drink any purple or red liquids. Instruct patients to tell you if they experience vomiting, dizziness, or decreased urination. This may be a sign that they have lost too much fluid while using OsmoPrep or Visicol. Instruct patients to tell you if they have trouble drinking liquids while taking OsmoPrep or Visicol or experience severe stomach cramping, bloating, nausea, or headache.

What should your patients avoid while taking OsmoPrep or Visicol?

- Patients should NOT take other medications containing sodium phosphate
- Patients should NOT use OsmoPrep or Visicol again within 7 days

What are the possible adverse effects of OsmoPrep and Visicol?

Rare but serious adverse effects can occur while taking or after taking OsmoPrep or Visicol. These include

- Renal failure resulting in permanent impairment of renal function sometimes requiring long-term dialysis
- Severe dehydration
- Seizures or blackouts
- Cardiac arrhythmias
- Electrolyte disturbances

Other serious adverse effects seen postapproval include

- Hypersensitivity reactions such as anaphylaxis, rash, pruritus, urticaria, throat tightness, bronchospasm, dyspnea, pharyngeal edema, dysphagia, paresthesia and swelling of the lips, and facial swelling
- Renal impairment, increased blood urea nitrogen (BUN), increased creatinine, and renal tubular necrosis

The most common adverse effects of OsmoPrep or Visicol reported in clinical trials are

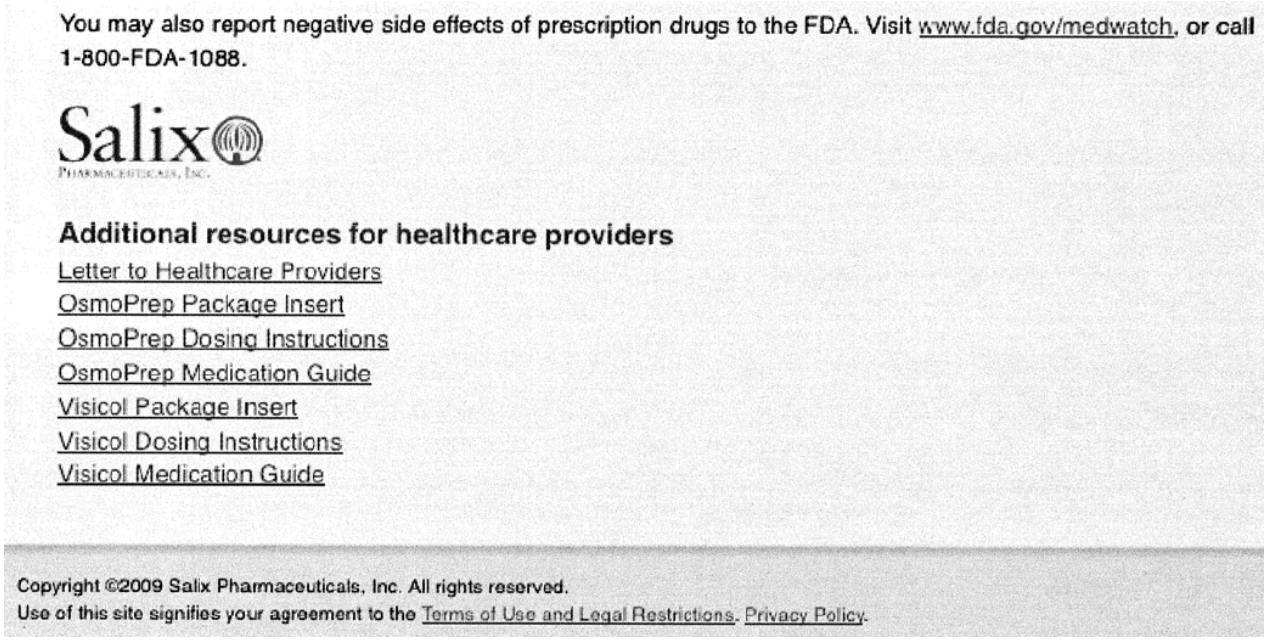
- Bloating
- Nausea
- Abdominal pain
- Vomiting

Please review the full package insert for additional information; for links, see below.

Contact us with your concerns.

Salix Pharmaceuticals is dedicated to patient safety and to addressing concerns you may have regarding the administration of our products. Should you have any questions, please contact us by phone at (866)-669-SLXP (7597) or by e-mail at prephelp@salix.com.

For product information, adverse event reports, and product complaint reports please call
Salix Product Information Call Center
Phone: 1-800-508-0024
Fax: 1-510-595-8183
E-mail: Salix@medcomsol.com



You may also report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Salix
Pharmaceuticals, Inc.

Additional resources for healthcare providers

Letter to Healthcare Providers
OsmoPrep Package Insert
OsmoPrep Dosing Instructions
OsmoPrep Medication Guide
Visicol Package Insert
Visicol Dosing Instructions
Visicol Medication Guide

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21097	SUPPL-14	SALIX PHARMACEUTICALS INC	VISICOL(SODIUM PHOSPHATE DIBASIC ANHYDRA
NDA-21892	SUPPL-4	SALIX PHARMACEUTICALS INC	OSMOPREP

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

/s/

JOYCE A KORVICK
10/13/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-014

NDA 21-892/S-004

REMS

NDA 21-097 Visicol® (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets

NDA 21-892 OsmoPrep® (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1 GOAL(S)

The goal of the REMS for Visicol and OsmoPrep (sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous) Tablets is to communicate the risks of acute phosphate nephropathy associated with the use of oral sodium phosphate products to healthcare professionals and patients.

2 REMS ELEMENTS

2.1 MEDICATION GUIDE

A Medication Guide will be dispensed with each Visicol and OsmoPrep prescription in accordance with 21 CFR 208.24. The appropriate number of Medication Guides along with the approved package insert will be provided directly to the pharmacy with each bottle of OsmoPrep and Visicol. Any multi-dose bottle will be shipped in a carton with multiple Medication Guides enclosed to allow dissemination to each patient. Product labels will prominently state that the Medication Guide should be dispensed to each patient.

All professional samples given to patients by a healthcare professional shall include a Medication Guide adhered to the primary packaging to ensure that the safety information is distributed to the patient.

The Medication Guide is appended.

2.2 COMMUNICATION PLAN

Salix will implement a communication plan to healthcare providers to support the implementation of the REMS. Salix will continue the communication plan until January 1, 2013.

2.2.1 Dear Healthcare Professional Letter

A Dear Healthcare Professional (DHCP) letter will be disseminated within 60 days of REMS approval and will include the revised prescribing information and Medication Guide. It will be distributed to healthcare professionals in family medicine, internal medicine, general surgery, gastroenterology, general practice, nephrology, colorectal surgery, and others who have prescribed or dispensed Visicol and/or OsmoPrep, performed follow-up assessments of patients following administration, or have been called on by Salix sales representatives within the past year.

The DHCP Letter, Medication Guide, and prescribing information will also be made available to approximately 70,000 national and regional pharmacies electronically and via e-mail to pharmacists and pharmacy technicians so that dispensers of the products are fully informed of the updated safety information and safe use of Visicol and OsmoPrep.

The Dear Healthcare Professional Letter is appended.

2.2.2 Educational Product Website

Salix will utilize the searchable online product website www.warninginfoforosmoprepandvisicol.com dedicated to inform and educate healthcare professionals on the safety, proper administration and use of Visicol and OsmoPrep Tablets.

The product website will include:

- Questions and answers regarding acute phosphate nephropathy, safety information and the safe use of OsmoPrep and Visicol
- A copy of the Dear Healthcare Professional Letter
- A copy of the Medication Guide for each product
- A copy of the current package insert for each product
- Suggested dosing regimen for each product
- Adverse event reporting contact

3 ELEMENTS TO ASSURE SAFE USE

This REMS for Visicol and OsmoPrep Tablets does not include elements to assure safe use.

4 IMPLEMENTATION SYSTEM

An implementation system is not required because this REMS for Visicol and OsmoPrep Tablets does not include elements to assure safe use.

5 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Salix will submit REMS Assessments to FDA 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Salix will submit each assessment so that it will be received by the FDA on or before the due date.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-014

NDA 21-892/S-004

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type	Prior Approval Supplement Safety Labeling Changes under 505(0)(4)
Application Number(s)	NDA 21-097 and 21-892
Priority or Standard	Standard
Submit Date(s)	January 8, 2009
Received Date(s)	January 9, 2009
Amended PDUFA Goal Date	March 10, 2009
Reviewer Name(s)	Christopher Leptak, MD/PhD
Review Completion Date	March 13, 2009
Established Name	Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP
Trade Name	Visicol and Osmoprep
Therapeutic Class	Purgative
Applicant	Salix Pharmaceuticals, Inc.
Indication(s)	Bowel Cleansing Preparation Prior to Colonoscopy
Intended Population(s)	Patients undergoing annual screening and /or diagnostic colonoscopy

Clinical Review Addendum

This review is intended to augment the primary clinical review by Eric Wynn. Additional information will include a summary of the comments and recommendations from the consultative disciplines as well as additional actions that took place since my assignment to the project starting February 16, 2009. Of note, the information included is applicable to both the Osmoprep and Visicol drug products.

I. Consults

1. Division of Drug Marketing, Advertising, and Communications (DDMAC) and Division of Risk Management (DRISK)

The consult's review, comments, and recommendations were shared in the Memorandum dated February 12, 2009. The comments were based on the proposed package inserts (PIs) and medication guides (MGs) submitted by the Sponsor on January 8, 2009. Of note, the comments were inclusive upon review of the entire proposed PI and thus included comments to sections that were not identified as areas of safety concern by Joyce Korvick, Deputy Director of Safety for the Division of Gastroenterology Products (DGP) in her letter dated December 10, 2008. Upon internal discussion on March 2, 2009, it was agreed upon that the recommendations pertinent to the identified safety issue would be addressed at this time while any additional comments would be shared with the sponsor at a later date. The main safety signal pertinent comments are summarized below with internal discussion and agreements *italicized*.

a. Package Insert (PI)

Boxed Warning

1. Include context for the modified "rare" regarding the number of case reports or delete all together. *Based on the information provided through AERs reports and input from OSE, the use of rare is the best modifier that accurately reflects the cases at this time.*
2. Clarification of the age description for the targeted patient population. *The removal of a specific age lower limit was discussed previously and the proposal of "increased age" is best representative of the reported cases.*

Warnings

1. Provide context to patient population in which fatalities have occurred. *Given that hydration status secondary to the loss of fluid during the colonoscopy prep is potentially a contributing factor to the reported adverse events, we came to internal alignment that the following phrase should be included: "It is recommended that patients receiving (Drug Name) be advised to adequately hydrate before, during, and after the use of (Drug Name)."*

2. "Renal disease, acute phosphate nephropathy, and electrolyte disorders." *To give a time to event context, we decided to provide the following additional language:*

"The time to onset for these events ranged from a few days to several months after the ingestion of these products." This time frame was based upon OSE's review of the reported cases.

b. Medication Guide (MG)

"Serious kidney (b) (4) DDMAC and DRISK asked for guidance regarding to the time to onset of events. *Given the description included in the PI, agreement was reached to include the following language: "These kidney problems can sometimes lead to kidney failure or the need for dialysis for a long time. These problems can happen within a few days to months after taking (Drug Name)."*

"What should I tell my doctor before taking (Drug Name)?" DDMAC and DRISK requested language regarding the use of alcohol with these products. *DGP initially proposed specific signs and symptoms for alcohol withdrawal, but agreement was reached to simply the discussion to tell your doctor "if you drink alcohol." This gives the doctor the opportunity to access if a patient's drinking may predispose s/he to an increased risk of seizures or electrolyte imbalances.*

"Tell your doctor about all the medications you take." Clarification is needed from the Sponsor regarding "(b) (4)." *The subset of medications focusing on (b) (4) contributions to kidney disease is too limited since any medications for kidney impairment would be important for the doctor to know. Remove the clause (b) (4) from the description.*

"How should I take (Drug Name)?" New language was proposed by DDMAC and DRISK for clarity. *However, there was concerns voiced that the language was still not clear. Internal discussion led to the following:*
"1. Take (Drug Name) with 8 ounces of clear liquids
2. Wait 15 minutes.
3. Take (more of Drug Name) with 8 ounces of clear liquids.
4. Repeat steps 2 and 3 above, three more times. Make sure you wait 15 minutes after each time."

II. Action: Teleconference with Salix March 9, 2009

After discussion with Salix, the final package inserts and medication guides for both Visicol and OsmoPrep were agreed upon.

III. Recommendation

This reviewer agrees with the language included in the final package inserts and medication guides. For the open REMS for both Visicol and OsmoPrep, the PIs and MGs are now complete. The remaining items still under review and negotiation are the

medical community correspondence letter, an information website, and a prospective study proposal to address the acute phosphate nephropathy safety issue.

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

/s/

Christopher L Leptak
3/24/2009 01:01:23 PM
MEDICAL OFFICER

Joyce Korvick
3/24/2009 05:34:06 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-014
NDA 21-892/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Scherer, Matthew

From: Scherer, Matthew
Sent: Friday, September 04, 2009 12:57 PM
To: 'Burgin, Benjamin'
Subject: OsmoPrep and Visicol (NDA 21-892, 21-097) - requested revisions to REMS and DHCP letter

Attachments: 09-04-09 REMS and DHCP letter with requested revisions.pdf

Benjamin,

Attached, please find a document that contains the requested revisions to the OsmoPrep and Visicol REMS and DHCP letters. These revisions supersede those sent to you on September 2, 2009. Please revise as requested and resubmit the compete REMS.

Best regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

10903 New Hampshire Avenue
Building 22, Room 5137
Silver Spring, MD 20993

09-04-09 REMS and DHCP letter ...

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21097	SUPPL-14	SALIX PHARMACEUTICALS INC	VISICOL(SODIUM PHOSPHATE DIBASIC ANHYDRA
NDA-21097	SUPPL-14	SALIX PHARMACEUTICALS INC	VISICOL(SODIUM PHOSPHATE DIBASIC ANHYDRA
NDA-21892	SUPPL-4	SALIX PHARMACEUTICALS INC	OSMOPREP
NDA-21892	SUPPL-4	SALIX PHARMACEUTICALS INC	OSMOPREP

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/s/

MATTHEW C SCHERER
09/04/2009

Scherer, Matthew

From: Scherer, Matthew
Sent: Monday, June 29, 2009 2:19 PM
To: 'Glifort, Gail'
Subject: Comments from FDA re: OsmoPrep and Visicol REMS (NDAs 21-892, 21-097)

Dear Ms. Glifort:

Please refer to your February 9, 2009 Risk Evaluation and Mitigation Strategy (REMS) submission for NDA 21-097 for Visicol (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets and NDA 21-892 for OsmoPrep (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your REMS.

Medication Guide:

1. The Medication Guide distribution procedure is not acceptable. The use of (b) (4) Medication Guides are required to be disseminated with each new or refill prescription. Using (b) (4) would not guarantee that the Medication Guides are available for distribution at all pharmacies. Moreover, FDA learned in a recent study on Consumer Medication Information that (b) (4) Medication Guides must follow and be printed in the approved format and content as specified in 21 CFR 208.20. Revise and resubmit a Medication Guide distribution procedure that ensures sufficient numbers of Medications Guides will be provided with the product such that each patient will receive a printed, hard-copy of the approved Medication Guide. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

    - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
    - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

2. We remind you of the requirement to comply with 21 CFR 208.24. A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use): "Dispense the enclosed Medication Guide to each patient." or "Dispense the accompanying Medication Guide to each patient."

Communication Plan:

3. Your proposal states that you plan to send the Dear Health Care Professional Letter to various physicians based on their specialty, as well as those involved in the prescribing or dispensing of Visicol and OsmoPrep and/or follow–up assessments of patients following bowel cleansing. Please describe the exact mechanism(s) you will use to identify these providers.

4. The Dear Healthcare Professional Letter, Prescribing Information and Medication Guide will be made available electronically to approximately 70,000 retail and non-retail pharmacies. Please describe how you will locate these pharmacies, and by what means the pharmacies will be alerted regarding the availability of the educational materials. Please include information on how rural, mail order and specialty pharmacies will be included in the list of pharmacies.

5. Describe the mechanism through which the DCHP letter, PI, and Medication Guide will be made available electronically to retail and non-retail pharmacies.

6. Ensure that the proposed website name is searchable. Also, provide a link to the proposed website off of your main

website.

7. We believe the information that is included in the website would be valuable to send along with the DHCP letters. The letter at this point is limited to informing prescribers about the safety labeling changes but not about the safe use of OSP products.

Information Needed For Assessment (REMS Assessment Plan):

8. (b) (4)

9. Your REMS Assessment Plan should include a plan to assess physicians' and healthcare providers' (targeted in your communication plan) understanding of risks and safe use of Visicol and OsmoPrep. Submit in your supporting document your plan to conduct this assessment. If you plan to conduct this assessment using a survey, submit for review all methodology and instruments used to measure physicians' and HCPs' understanding of the risks and safe use of Visicol and OsmoPrep. The methodology should be submitted at least 90 days prior to conducting the surveys. This should include, *but not be limited to:*
    a. Sample size and confidence interval associated with that sample size
    b. How the sample will be determined (selection criteria)
    c. The expected number of participants surveyed
    d. How the participants will be recruited
    e. How and how often the surveys will be administered
    f. Explain controls used to minimize bias
    g. Explain controls used to compensate for the limitations associated with their methodology
    h. You should submit the survey instruments (questionnaires and moderator's guide) for review.
    i. Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys

10. Prominently identify any future submissions containing changes to the survey or methodology with the following wording in bold capital letters at the top of the first page of the submission:

<<insert application #>>
REMS OTHER

General Comments:

11. We remind you that REMS materials are not appropriate for use in a promotional manner.

12. Resubmission Requirements: Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document. Please submit any additional communication and/or educational materials to the agency for review. These should be formatted mock-ups.

Please contact me is you have any questions.

Best Regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

10903 New Hampshire Avenue
Building 22, Room 5137
Silver Spring, MD 20993

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

/s/

Matthew Scherer
6/29/2009 02:22:30 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Nina Ton, Pharm.D.
Safety Regulatory Manager
OSE

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Kristen Everett, Safety Regulatory Manager, DGP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 23, 2009		21-892 21-097	RP	February 9, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Visicol and OsmoPrep	FDAAA - REMS	cathartics/bowel cleanse	June 1, 2009

NAME OF FIRM: Salix Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DGP requests your expertise in the review of the REMS documents submitted for the oral sodium phosphate products, OsmoPrep and Visicol. The documents are available in the GI eRoom/safety folder/ oral sodium phosphates/sponsor docs. The documents relevant to the REMS are the DHCP Letter, OsmoPrep REMS Plan, and REMS supporting document. The REMS documents cover BOTH products.

SIGNATURE OF REQUESTOR
Kristen Everett/Joyce Korvick

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Kristen Everett
4/23/2009 10:52:53 AM

Salix®
PHARMACEUTICALS, INC.

NDA 21-097/S-014

September 30, 2009

NDA 21- 097 SUPPLEMENT 014
PROPOSED REMS - AMENDMENT

Joyce Korvick, MD
Deputy Director
Division of Gastroenterology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 21-097/S-014, Amendment 4**
Visicol® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets
Prior Approval Supplement (PAS) – Proposed REMS

Dear Dr. Korvick:

In accordance with section 505(1)(a) of the Food, Drug, and Cosmetic Act and as required in the FDA action letter issued December 11, 2008, Salix Pharmaceuticals, Inc. (Salix) hereby submits for the Agency's review and approval, further revisions to the Risk Evaluation and Mitigation Strategy (REMS) for Visicol® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets, NDA 21-097.

On September 24, 2009, Salix submitted one revised REMS with appended material (i.e., Medication Guide, DHCP Letter, and Educational Product Website content) and the proposed REMS Supporting Document in accordance with requested revisions received from the Agency on September 4, 2009. In the submission, the OsmoPrep® Medication Guide was inadvertently appended to the Visicol REMS. Enclosed, please find the Visicol Medication Guide for inclusion in the REMS submitted to the Agency on September 24, 2009.

If there are any questions concerning this submission, please do not hesitate to contact me directly at (919) 447-3404 or by fax at (919) 447-3410. In the event of my absence, you may also contact David Dobrowski, Director, Regulatory Affairs at (919) 862-1047.

Sincerely,

Benjamin M. Burgin, RAC
Senior Manager, Regulatory Affairs

Salix® PHARMACEUTICALS, INC.

ORIGINAL

NDA 21-097/S-014
September 24, 2009

NDA 21- 097 SUPPLEMENT 014
PROPOSED REMS - AMENDMENT

Joyce Korvick, MD
Deputy Director
Division of Gastroenterology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED
SEP 25 2009
CDER CDR

SD-151

ORIGINAL

Subject: **NDA 21-097/S-014, Amendment 3**
Visicol® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets
Prior Approval Supplement (PAS) – Proposed REMS

Dear Dr. Korvick:

In accordance with section 505(1)(a) of the Food, Drug, and Cosmetic Act and as required in the FDA action letter issued December 11, 2008, Salix Pharmaceuticals, Inc. (Salix) hereby submits for the Agency's review and approval, further revisions to the Risk Evaluation and Mitigation Strategy (REMS) for Visicol® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets, NDA 21-097.

The originally proposed REMS was submitted to the Agency on February 9, 2009. Subsequent revisions to the REMS, REMS Supporting Document, and Dear Healthcare Professional (DHCP) letter were submitted to the Agency on July 30, 2009 and August 17, 2009 in accordance with FDA comments and requested revisions received by Salix on June 29, 2009.

On September 4, 2009, Salix received further requested revisions from the Agency for the REMS and DHCP Letter. In accordance with these requests, this submission contains one revised REMS with appended material (i.e., Medication Guide, DHCP Letter, and Educational Product Website content) and the proposed REMS Supporting Document. Additional editorial changes to the REMS have been made by Salix to omit duplicate information and ensure consistency of terminology. A CD is also enclosed which contains the REMS documentation in track changes and clean Word format.

If there are any questions concerning this submission, please do not hesitate to contact me directly at (919) 447-3404 or by fax at (919) 447-3410. In the event of my absence, you may also contact David Dobrowski, Director, Regulatory Affairs at (919) 862-1047.

Sincerely,

Benjamin M. Burgin, RAC
Senior Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

ORIGINAL

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Salix Pharmaceuticals, Inc.	09/24/2009 ORIGINAL
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(919) 862-1000	(919) 862-1095
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1700 Perimeter Park Drive Morrisville, NC 27560	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Not Applicable

RECEIVED
SEP 25 2009
CDER CDR

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-097

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
See Chemical Name	Visicol Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP

CODE NAME *(If any)*
INKP-101

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	1.5 grams	Oral

(PROPOSED) INDICATION(S) FOR USE:
Cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Visicol® Tablets Holder of Approved Application Salix Pharmaceuticals, Inc.

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amendment to S-014 Proposed REMS

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 21-892, IND 56,291, (b) (4)

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Revised REMS

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
for DD	David Dobrowski Director, Regulatory Affairs	24-Sep-2009

ADDRESS *(Street, City, State and ZIP Code)*	Telephone Number
1700 Perimeter Park Drive, Morrisville, NC 27560	(919) 862-1047

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

epartment of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Salix®
PHARMACEUTICALS, INC.

ORIGINAL

NDA 21-097/S-014

ORIGINAL

July 30, 2009

NDA 21- 097 SUPPLEMENT 014
PROPOSED REMS - AMENDMENT

Joyce Korvick, MD
Deputy Director
Division of Gastroenterology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

SD-149

RECEIVED
JUL 31 2009
CDR

Subject: **NDA 21-097/S-014, Amendment 1**
Visicol® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets
Prior Approval Supplement (PAS) – Proposed REMS

Dear Dr. Korvick:

In accordance with section 505(1)(a) of the Food, Drug, and Cosmetic Act and as required in the FDA action letter issued December 11, 2008, Salix Pharmaceuticals, Inc. (Salix) hereby submits for the Agency's review and approval, a revised Risk Evaluation and Mitigation Strategy (REMS) to Visicol® (Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets, NDA 21-097.

The originally proposed REMS was submitted on February 9, 2009. On June 29, a communication was sent to Salix by the FDA project manager, Matthew Scherer, which contained FDA comments and requested revisions of the REMS.

This submission contains one revised REMS for both OsmoPrep and Visicol as they are identical and the revised REMS Supporting Document. A disc is also enclosed which contains, as requested, the aforementioned documentation in track changes and clean WORD files.

If there are any questions concerning this submission, please do not hesitate to contact me at (919) 862-1055 or via facsimile at (919) 228-4255 or email Gail.Glifort@Salix.com.

Sincerely,
Salix Pharmaceuticals, Inc.

Gail Glifort

Gail Glifort, RAC
Senior Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Salix Pharmaceuticals, Inc.	07/30/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX) Number (Include Area Code)*
(919) 862-1000	(919) 862-1095 ORIGINAL
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
1700 Perimeter Park Drive Morrisville, NC 27560	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-097

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
See Chemical Name	Visicol Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP	INKP-101

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	1.5 grams	Oral

(PROPOSED) INDICATION(S) FOR USE:
Cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Visicol® Tablets Holder of Approved Application Salix Pharmaceuticals, Inc.

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amendment to S-014 Proposed REMS

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 21-892, IND 56,291, (b) (4)

RECEIVED
JUL 31 2009

CDR

This application contains the following items: *(Check all that apply)*

☐	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* REMS

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Neil Kluft for DD	David Dobrowski Director, Regulatory Affairs	30 July 2009

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1700 Perimeter Park Drive, Morrisville, NC 27560	(919) 862-1047

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Salix®
PHARMACEUTICALS, INC.

NDA 21-097/S-014

February 9, 2009

NEW SUPPLEMENT FOR NDA 21-097
PROPOSED REMS

Joyce Korvick, MD
Deputy Director
Division of Gastroenterology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 21-097/S-014**
Visicol® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets
Prior Approval Supplement (PAS) – Proposed REMS

Dear Dr. Korvick:

In accordance with section 505(1)(a) of the Food, Drug, and Cosmetic Act and as required in the FDA action letter issued December 11, 2008, Salix Pharmaceuticals, Inc. (Salix) hereby submits for the Agency's review and approval, a new supplement to Visicol® (Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets, NDA 21-097, containing a proposed Risk Evaluation and Mitigation Strategy (REMS).

In December 2008, the Food and Drug Administration (FDA) informed Salix of a letter being issued concerning the safety of its sodium phosphate tablets OsmoPrep® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) and Visicol® (Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP). This letter required, among other things, that Salix plan a REMS for OsmoPrep and Visicol.

This submission contains one REMS for both OsmoPrep and Visicol as they are identical; the proposed prescribing information and Medication Guide, currently under review with the Agency, are specific to Visicol. Also as part of the REMS, a proposed Dear Health Care Professional letter and REMS Supporting Document are included as well.

1700 Perimeter Park Drive, Morrisville, NC 27560 www.salix.com T • 919.862.1000 F • 919.862.1095

If there are any questions concerning this submission, please do not hesitate to contact me at (919) 862-1055 or via facsimile at (919) 228-4255 or email Gail.Glifort@Salix.com.

Sincerely,
Salix Pharmaceuticals, Inc.

Gail Glifort, RAC
Senior Manager, Regulatory Affairs

Salix®
PHARMACEUTICALS, INC.

ORIGINAL

NDA 21-892/S-004

February 9, 2009

NEW SUPPLEMENT FOR NDA 21-892
PROPOSED REMS

RECEIVED
FEB 10 2009
CDR

Joyce Korvick, MD
Deputy Director
Division of Gastroenterology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA NO. 21-892 REF NO. 004
NDA SUPPL FOR SLR

SUPPLEMENT AMENDMENT
SLR-004 (RP)

Subject: **NDA 21-892/S-004**
OsmoPrep® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets
Prior Approval Supplement (PAS) – Proposed REMS

Dear Dr. Korvick:

In accordance with section 505(1)(a) of the Food, Drug, and Cosmetic Act and as required in the FDA action letter issued December 11, 2008, Salix Pharmaceuticals, Inc. (Salix) hereby submits for the Agency's review and approval, a new supplement to OsmoPrep® (Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) Tablets, NDA 21-892, containing a proposed Risk Evaluation and Mitigation Strategy (REMS).

In December 2008, the Food and Drug Administration (FDA) informed Salix of a letter being issued concerning the safety of its sodium phosphate tablets OsmoPrep® (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP) and Visicol® (Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP). This letter required, among other things, that Salix plan a REMS for OsmoPrep and Visicol.

This submission contains one REMS for both OsmoPrep and Visicol as they are identical; the proposed prescribing information and Medication Guide, currently under review with the Agency, are specific to OsmoPrep. Also as part of the REMS, a proposed Dear Health Care Professional letter and REMS Supporting Document are included as well.

If there are any questions concerning this submission, please do not hesitate to contact me at (919) 862-1055 or via facsimile at (919) 228-4255 or email Gail.Glifort@Salix.com.

Sincerely,
Salix Pharmaceuticals, Inc.

Gail Glifort, RAC
Senior Manager, Regulatory Affairs