CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-013
NDA 21-892/S-003

Trade Name: Visicol (NDA 21-097/S-013)
OsmoPrep (NDA 21-892/S-003)

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

Sponsor: Salix Pharmaceuticals, Inc..

Approval Date: 3/25/2009

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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CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA 21-892/S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-097/S-013
NDA 21-892/S-003

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 supplemental new drug applications dated January 8, 2009, received January 9, 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.

Reference is also made to an FDA letter dated December 10, 2008 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Visicol and OsmoPrep. This information pertains to the risk of acute phosphate nephropathy, a form of acute kidney injury.

Your supplemental applications provide for revisions to the labeling for Visicol and OsmoPrep, consistent with our December 10, 2008 letter, and the discussion in the March 9, 2009 teleconference between FDA and Salix in which agreement was reached on these safety labeling changes.

We also acknowledge receipt of your submissions dated February 9, and March 10, 2009.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Your approved Medication Guides will become part of the Risk Evaluation and Mitigation Strategy (REMS) submitted in pending supplements NDA 21-097/S-014 and NDA 21-892/S-004.

CONTENT OF LABELING

The final printed labeling (FPL) must be identical to the enclosed labeling (package inserts and medication guides appended at the end of this letter.)

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package inserts and medication guides). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved supplements NDA 21-097/S-013, and NDA 21-892/S-003."**

Marketing the products with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

Please note that:

- this Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18) or 21 CFR 201.80(f)(2)];

- you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];

- the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)]

LETTER TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) other than the letter required as part of the REMS, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (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: Visicol Package Insert and Medication Guide
OsmoPrep Package Insert and Medication Guide

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

3/25/2009 11:05:45 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-013
NDA 21-892/S-003

LABELING

Visicol® Tablets

(sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP)

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 nonsteriodal anti-inflammatory drugs [NSAIDs]). *See* **WARNINGS**.

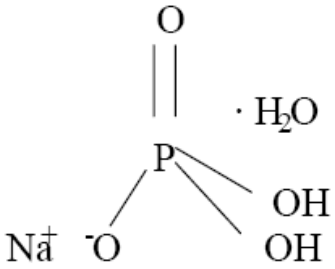
It is important to use the dose and dosing regimen as recommended (pm/am split dose). *See* **DOSAGE and ADMINISTRATION**.

DESCRIPTION

Visicol® (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP) is a purgative used to clean the colon prior to colonoscopy. Visicol® Tablets are white to off-white compressed tablets, with a monogram "I" on each side of the upper surface and a plain lower surface. Each tablet contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic anhydrous, USP for a total of 1.5 grams of sodium phosphate per tablet. Inert ingredients include microcrystalline cellulose (MCC), NF; magnesium stearate, NF; and colloidal silicon dioxide, NF. Visicol® is gluten-free.

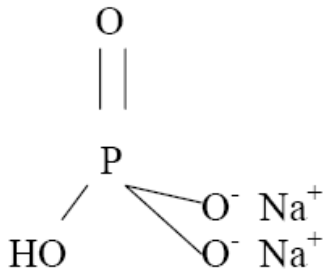
The structural and molecular formulae and molecular weights of the active ingredients are shown below:

- Sodium phosphate monobasic monohydrate, USP



Molecular Formula: $NaH_2PO_4 \cdot H_2O$
Molecular Weight: 137.99

- Sodium phosphate dibasic anhydrous, USP



Molecular Formula: Na_2HPO_4
Molecular Weight: 141.96

Visicol® Tablets are for oral administration only.

CLINICAL PHARMACOLOGY

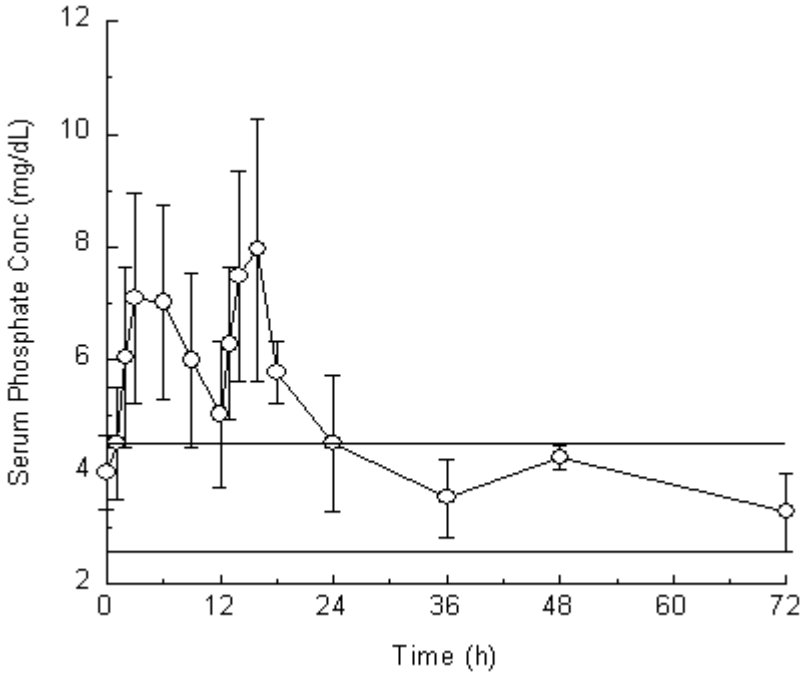
Visicol® Tablets, taken in two doses of 30 grams (the complete regimen contains a total of 60 grams of sodium phosphate) approximately twelve hours apart, induces diarrhea, which effectively cleanses the entire colon. Each administration has a purgative effect for approximately 1 to 3 hours. The primary mode of action is thought to be through osmotic action of sodium, causing large amounts of water to be drawn into the colon, promoting colon evacuation.

Pharmacokinetics

An open-label pharmacokinetic study of Visicol® in healthy volunteers was performed to determine the concentration-time profile of serum inorganic phosphorus levels after Visicol® administration. All subjects received a total of 60 grams of sodium phosphate with a total liquid volume of 3.6 quarts. Subjects received a 30 gram dose (20 tablets given as 3 tablets every 15 minutes with 8 ounces of clear liquids) beginning at 6 PM and then received a second 30 gram dose (20 tablets given as 3 tablets every 15 minutes with 8 ounces of clear liquids) the following morning beginning at 6 AM.

Twenty-three healthy subjects (mean age 57 years old; 57% male and 43% female; and 65% Hispanic, 30% Caucasian, and 4% African-American) participated in this pharmacokinetic study. The serum phosphorus level rose from a mean (± standard deviation) baseline of 4.0 (± 0.7) mg/dL to 7.7 (± 1.6 mg/dL), at a median of 3 hours after the administration of the first 30 gram dose of Visicol® Tablets (see Figure 1).

Figure 1. Mean (± standard deviation) serum phosphorus concentrations



The serum phosphorus level rose to a mean of 8.4 (± 1.9) mg/dL, at a median of 4 hours after the administration of the second 30 gram dose of Visicol® Tablets. The serum phosphorus level remained above baseline for a median of 24 hours after the administration of the initial dose of Visicol® Tablets (range 16 to 48 hours).

The upper (4.5 mg/dL) and lower (2.6 mg/dL) reference limits for serum phosphate are represented by solid bars.

Special Populations

Renal insufficiency: The effect of renal dysfunction on Visicol® Tablets pharmacokinetics has not been studied. Since the inorganic form of phosphate in the circulating plasma is excreted almost entirely by the kidneys, patients with renal disease may have difficulty excreting a large phosphate load. Thus, Visicol® Tablets should be used with caution in patients with impaired renal function **(see WARNINGS)**.

Hepatic insufficiency: Visicol® Tablets have not been investigated in patients with hepatic failure. Visicol® is not expected to be metabolized in the liver.

Geriatric: In a single pharmacokinetic study of sodium phosphate tablets, which included 6 elderly volunteers, plasma half-life increased two-fold in subjects > 70 years of age compared to subjects < 50 years of age (3 subjects and 5 subjects, respectively).

Gender: No difference in serum phosphate AUC values were observed in the single pharmacokinetic study conducted with Visicol® in 13 male and 10 female healthy volunteers.

CLINICAL STUDIES

A total of 957 adult patients were enrolled and treated in the controlled clinical trials of Visicol® Tablets. Males and females were about equally represented. Approximately 87% of the study population was Caucasian. Visicol® Tablets were found to be comparable in cleansing efficacy to the comparison drug, a commercially available polyethylene glycol-salt (PEG-salt solution) solution (Cherry Flavor NuLYTELY®). Two identical, single (investigator) blind, randomized, multicenter trials were conducted comparing the efficacy and safety of Visicol® Tablets and the PEG-salt solution comparator as a colon cleansing agent in patients undergoing routine diagnostic colonoscopy. In each study, over 200 patients were randomized to self-administer the Visicol® Tablets and over 200 were randomized to self-administer the PEG-salt solution comparator. Colonoscopy was generally performed within 5 hours of the second dose. Physicians used a four-point, validated Physician Questionnaire to assess efficacy. The distribution of "excellent", "good", "fair" and "inadequate", as evaluated by the physician performing the colonoscopy, was comparable in both groups. Cleansing efficacy observed in these studies is described in Table 1.

Table 1: Observed overall colon cleansing efficacy of Visicol® Tablets versus PEG-salt solution comparator in the all assessed patient population

	Study A		Study B	
Efficacy Rating	Visicol Tablets **n** (%)	PEG-salt solution Comparator **n** (%)	Visicol Tablets **n** (%)	PEG-salt solution Comparator **n** (%)
Excellent or Good	**171** (82.2)	**156** (75.4)	**183** (86.3)	**170** (78.0)
Fair	**34** (16.3)	**49** (23.7)	**26** (12.3)	**45** (20.6)
Inadequate	**3** (1.4)	**2** (1.0)	**3** (1.4)	**3** (1.4)
Total patients	**208**	**207**	**212**	**218**
p value†	n.s.		n.s.	

† p values (Cochran-Mantel-Haenszel Test) were calculated for comparisons between Excellent and Good versus Fair versus Inadequate; Visicol® Tablets and PEG-salt solution comparator.

The efficacy of overall colonic cleansing with the Visicol® Tablets was comparable to the PEG-salt solution. In addition, the incidence of "Inadequate" colon cleansing ratings due to poor purgative preparation was similar between Visicol® Tablets and the PEG-salt solution comparator. Also, cleansing efficacy in the ascending colon with Visicol® Tablets was comparable to the PEG-salt solution.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Visicol® Tablets are contraindicated in patients with biopsy-proven acute phosphate nephropathy.

Visicol® Tablets are contraindicated in patients with a known allergy or hypersensitivity to sodium phosphate salts or any of its ingredients.

WARNINGS

Administration of sodium phosphate products prior to colonoscopy has resulted in fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias. These fatalities have been observed in patients with renal insufficiency, in patients with bowel perforation, and in patients who misused or overdosed sodium phosphate products. It is recommended that patients receiving Visicol®be advised to adequately hydrate before, during, and after the use of Visicol®.

Considerable caution should be advised before Visicol® Tablets are used in patients with the following illnesses: severe renal insufficiency (creatinine clearance less than 30 mL/minute), congestive heart failure, ascites, unstable angina, acute bowel obstruction, bowel perforation, toxic megacolon, gastric retention, ileus, pseudo-obstruction of the bowel, severe chronic constipation, acute colitis, gastric bypass or stapling surgery or hypomotility syndrome.

Consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in patients who may be at increased risk for serious adverse events, including those with history of renal insufficiency, history of ─ or at greater risk of ─ acute phosphate nephropathy, known or suspected electrolyte disorders (such as dehydration), seizures, arrhythmias, cardiomyopathy, prolonged QT, recent history of a MI and those with known or suspected hyperphosphatemia, hypocalcemia, hypokalemia, and hypernatremia. Also if patients develop vomiting and/or signs of dehydration then measure post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN).

Renal Disease, Acute Phosphate Nephropathy, and Electrolyte Disorders
There have been rare, but serious reports of renal failure, acute phosphate nephropathy, and nephrocalcinosis in patients who received oral sodium phosphate products (including oral sodium phosphate solutions and tablets) for colon cleansing prior to colonoscopy. These cases often resulted in permanent impairment of renal function and several patients required long-term dialysis. The time to onset is typically within days; however, in some cases, the diagnosis of these events has been delayed up to several months after the ingestion of these products. Patients at increased risk of acute phosphate nephropathy may include patients with the following: hypovolemia, baseline kidney disease, increased age, and patients using medicines that affect renal perfusion or function [such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs).

Use Visicol® with caution in patients with impaired renal function, known or suspected electrolyte disturbances (such as dehydration), or people taking concomitant medications that may affect electrolyte levels (such as diuretics). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have them corrected before treatment with Visicol® Tablets.

Seizures
There have been rare reports of generalized tonic-clonic seizures and/or loss of consciousness associated with use of sodium phosphate products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia) and low serum osmolality. The neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities. Visicol® should be used with caution in patients with a history of seizures and in patients at higher risk of seizure [patients using concomitant medications that lower the seizure threshold (such as tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, or patients with known or suspected hyponatremia].

Cardiac Arrhythmias
There have been rare, but serious reports of arrhythmias associated with the use of sodium phosphate products. Visicol® should be used with caution in patients with higher risk of arrhythmias (patients with a history of cardiomyopathy, patients with prolonged QT, patients with a history of uncontrolled arrhythmias, and patients with a recent history of a myocardial infarction). Pre-dose and post-colonoscopy ECGs should be considered in patients with high risk of serious, cardiac arrhythmias.

PRECAUTIONS

General

Patients should be instructed to drink 8 ounces of clear liquids with each 3-tablet (or each 2-tablet) dose of Visicol®. Patients should take a total of 3.6 quarts of clear liquids with Visicol®. Inadequate fluid intake, as with any effective purgative, may lead to excessive fluid loss and hypovolemia. Dehydration from purgation may be exacerbated by inadequate oral fluid intake, vomiting, and/or the use of diuretics. Patients should not take additional laxatives or purgatives, particularly additional sodium phosphate-based products.

Prolongation of the QT interval has been observed in some patients who were dosed with Visicol® Tablets. QT prolongation with Visicol® Tablets has been associated with electrolyte imbalances, such as hypokalemia and hypocalcemia. Visicol® Tablets should be used with caution in patients who are taking medications known to prolong the QT interval, since serious complications may occur. Pre-dose and post-colonoscopy ECGs should be considered in patients with known prolonged QT. In these studies, prolongation of the QT interval was also observed in some patients treated with PEG-salt solution.

Patients with a history of swallowing difficulties or anatomic narrowing of the esophagus, such as a stricture, may have difficulty swallowing Visicol® Tablets. Undigested or partially digested Visicol® Tablets may be seen in the stool or during colonoscopy. In addition, undigested tablets from other medications may be seen in the stool or during colonoscopy.

Administration of Visicol® Tablets may induce colonic mucosal aphthous ulcerations, since this endoscopic finding observed with other sodium phosphate cathartic preparations. This colonoscopic finding should be considered in patients with known or suspect inflammatory bowel disease (IBD).

Because published data suggest that sodium phosphate absorption may be enhanced in patients experiencing an acute exacerbation of IBD, Visicol® Tablets should be used with caution in IBD patients.

Since Visicol® Tablets were not studied in patients who recently had cardiac surgery (including coronary artery bypass graft surgery) Visicol® should be used with caution in these patients.

Drug Interactions

Medications administered in close proximity to Visicol® Tablets may not be absorbed from the gastrointestinal tract due to the rapid intestinal peristalsis and watery diarrhea induced by the purgative agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Visicol®. Studies to evaluate the effect of Visicol®on fertility or its mutagenic potential have not been performed.

Pregnancy

Category C. Reproduction studies have not been conducted with Visicol®. It is also not known whether Visicol® can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Visicol® Tablets should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and efficacy of Visicol® Tablets have not been demonstrated in patients less than 18 years of age.

Geriatric Use

Of the 980 subjects/patients in the Visicol® studies, 284 (29%) subjects/patients were 65 years of age or older. Of the 548 subjects/patients who received Visicol® in these studies, 146 (27%) were 65 years of age or older and 42 (8%) subjects/patients were 75 years of age or older.

In two phase 3 Visicol® trials (Study A and Study B), no overall differences in safety or effectiveness were observed between geriatric patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out; therefore, Visicol® Tablets should be used with caution in geriatric patients.

Sodium phosphate is known to be substantially excreted by the kidney, and the risk of adverse reactions with sodium phosphate may be greater in patients with impaired renal function. Since geriatric patients are more likely to have impaired renal function, consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in these patients (see **WARNINGS).**

ADVERSE REACTIONS

In the phase 3 Visicol® trials, bloating, nausea, abdominal pain, and vomiting were the most common drug-related adverse events reported with the use of Visicol® (see Table 2). Since diarrhea was considered as a part of the efficacy of Visicol® diarrhea was not defined as an adverse event in the clinical trials. Small superficial mucosal ulcerations, typical of those previously reported from the use of liquid preparations of sodium phosphate, and instances of mucosal bleeding have been observed on colonoscopy.

No patient in the clinical studies developed predefined postural changes in vital signs with concomitant symptoms of lightheadedness or syncope.

Table 2: Frequency of drug-related* adverse events (≥ 2%) of patients in the phase 3 Visicol trials (Studies A and B)

	Visicol® %=n/N	**NuLYTELY® %=n/N**

	N=427	N=432
Bloating	47%	61%
Nausea	35%	54%
Abdominal Pain	30%	36%
Vomiting	7%	18%

* Drug-related were adverse events possibly or probably drug-related

Electrolyte Changes

In Visicol® trials, changes in serum electrolytes (including phosphate, calcium, potassium, and sodium) have been observed in patients taking Visicol® Tablets.

In the Visicol® phase 3 trials, 96% and <1% of patients who took Visicol® (60 grams) and NuLYTELY® (up to 4 liters), respectively, developed hyperphosphatemia (defined as phosphate level > 4.7 mg/dL) on the day of the colonoscopy. In these trials, patients who took Visicol® and NuLYTELY® had baseline mean phosphate levels of 3.3 and 3.4 mg/dL and subsequently developed on the day of the colonoscopy mean phosphate levels of 7.1, and 3.3 mg/dL, respectively.

Two to three days after colonoscopy, 34%, 66%, and 0% of patients who received Visicol® had (reactive) hypophosphatemia (defined as phosphate level < 2.4 mg/dL), normal phosphate levels, and hyperphosphatemia, respectively. Two to three days after colonoscopy, 3%, 96%, and 1% of patients who received NuLYTELY® had (reactive) hypophosphatemia normal phosphate levels, and hyperphosphatemia, respectively. Two to three days after colonoscopy, patients who took Visicol® and NuLYTELY® had mean phosphate levels of 2.6 and 3.3 mg/dL, respectively.

In the Visicol® phase 3 trials, 47% and 9% of patients who took Visicol® and NuLYTELY®, respectively, developed hypocalcemia (defined as calcium level < 8.6 mg/dL) on the day of the colonoscopy. The mean changes in calcium levels (from baseline) for the Visicol® and NuLYTELY® patients were -0.6 and -0.1 mg/dL, respectively. Furthermore, in these trials, 28% and 3% of patients who took Visicol® and NuLYTELY®, respectively, developed hypokalemia (defined as potassium level < 3.5 mEq/L) on the day of the colonoscopy. The mean changes in potassium levels (from baseline) for the Visicol® and NuLYTELY® patients were -0.5 and -0.1 mEq/L, respectively. None of the patients who developed hypocalcemia or hypokalemia in the trials required treatment.

Postmarketing Experience

In addition to adverse events reported from clinical trials, the following adverse events have been identified during post-approval use of Visicol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to Visicol, or a combination of these factors.

General: Hypersensitivity reactions including anaphylaxis, rash, pruritus, urticaria, throat tightness, bronchospasm, dyspnea, pharyngeal edema, dysphagia, paresthesia and swelling of the lips and tongue, and facial swelling.

Cardiovascular: Arrhythmias

Nervous system: Seizures

Renal: Renal impairment, increased blood urea nitrogen (BUN), increased creatinine, acute renal failure, acute phosphate nephropathy, nephrocalcinosis, and renal tubular necrosis

OVERDOSAGE

There have been no reported cases of overdosage with Visicol® Tablets. Purposeful or accidental ingestion of more than the recommended dosage of Visicol® Tablets might be expected to lead to severe electrolyte disturbances, including hyperphosphatemia, hypocalcemia, hypernatremia, or hypokalemia, as well as dehydration and hypovolemia, with attendant signs and symptoms of these disturbances. Certain severe electrolyte disturbances may lead to cardiac arrhythmias, seizure, renal failure, and death. The patient who has taken an overdosage should be monitored carefully, and treated symptomatically for complications until stable.

DOSAGE AND ADMINISTRATION

The recommended dose of Visicol® Tablets for colon cleansing for adult patients is 40 tablets (60 grams of sodium phosphate) taken orally with a total of 3.6 quarts of clear liquids in the following manner:

> **The evening before the colonoscopy procedure:** Take 3 Visicol® Tablets (the last dose will be 2 Visicol® Tablets) with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets.
>
> **On the day of the colonoscopy procedure:** Starting 3-5 hours before the procedure, take 3 Visicol® Tablets (the last dose will be 2 Visicol® Tablets) with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets.

It is recommended that patients receiving Visicol® be advised to adequately hydrate before, during, and after the use of Visicol®.

Patients should not use Visicol® within seven days of previous administration. No additional enema or laxative is required, and patients should be advised NOT to take additional agents, particularly those containing sodium phosphate.

HOW SUPPLIED

Visicol® Tablets are supplied in child-resistant bottles containing 40 tablets and 100 tablets. Each tablet contains 1.102 g sodium phosphate monobasic monohydrate, USP and 0.398 g sodium phosphate dibasic anhydrous, USP for a total of 1.5 g of sodium phosphate per tablet. Each bottle contains two silica desiccant packets, which are not to be ingested.

NDC 65649-601-04 (40 tablets)
NDC 65649-601-41 (100 tablets)

Rx only

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Discard any unused portion.

Manufactured by:
Pharmaceutical Manufacturing Research Services Inc.
Horsham, PA 19044
For:
Salix Pharmaceuticals, Inc.
Morrisville, NC 27560

VENART 110-1/Mar 2009

Product protected by U.S. Patent No. 5,616,346 and other pending applications.

Medication Guide

VISICOL® (Vĭ-zə-käl)
sodium phosphate monobasic monohydrate, USP and
sodium phosphate dibasic anhydrous, USP)
Tablets

Read the Medication Guide that comes with VISICOL before you start taking it and each time you take it. This Medication Guide does not take the place of talking with your doctor about your condition or your treatment. If you have any questions about VISICOL, ask your doctor or pharmacist.

What is the most important information I should know about VISICOL?
VISICOL can cause serious side effects, including:

Serious kidney problems. Rare, but serious kidney problems can happen in people who take medicines made with sodium phosphate, including VISICOL, to clean your colon before a colonoscopy. These kidney problems can sometimes lead to kidney failure or the need for dialysis for a long time. These problems often happen within a few days, but sometimes may happen several months after taking VISICOL.

Conditions that can make you more at risk for having serious kidney problems with VISICOL include if you:

- lose too much body fluid (dehydration)
- have slow moving bowels
- have bowels blocked with stool (constipation)
- have severe stomach pain or bloating
- have any disease that causes bowel irritation (colitis)
- have kidney disease
- have heart failure
- take water pills or non-steroidal anti-inflammatory drugs (NSAIDS).

Your age may also affect your risk for having kidney problems with VISICOL.

Before you start taking VISICOL, tell your doctor if you:

- have any kidney problems.
- take any medicines for blood pressure, heart disease, or kidney disease.

Severe fluid loss (dehydration). People who take medicines that contain sodium phosphate can have severe loss of body fluid, with severe changes in body salts in the blood, and abnormal heart rhythms. These problems can lead to death.

Tell your doctor if you have any of these symptoms of loss of too much body fluid (dehydration) while taking VISICOL:

- vomiting
- dizziness
- urinating less often than normal
- headache

See "What are the possible side effects of VISICOL?" for more information about side effects.

What is VISICOL?

VISICOL is a prescription medicine used in adults 18 years and older, to clean your colon before a colonoscopy. VISICOL cleans your colon by causing you to have diarrhea. Cleaning your colon helps your doctor see the inside of your colon more clearly during the colonoscopy.

It is not known if VISICOL is safe and works in children under age 18.

Who should not take VISICOL?

Do not take VISICOL if:

- you have had a kidney biopsy that shows you have kidney problems because of too much phosphate
- you are allergic to sodium phosphate salts or any of the ingredients in VISICOL. See the end of this Medication Guide for a list of ingredients in VISICOL.

What should I tell my doctor before taking VISICOL?

Before taking VISICOL, tell your doctor about all your medical conditions, including if you have:

- any of the medical conditions listed in the section "What is the most important information I should know about VISICOL?"
- irritation of the bowel (colitis). VISICOL can cause symptoms of irritable bowel disease to flare-up.
- damage to your bowels
- had stomach surgery
- trouble swallowing pills. You may have trouble swallowing VISICOL.
- problems with an abnormal heart beat
- had a recent heart attack or have other heart problems
- symptoms of too much body fluid loss (dehydration) including vomiting, dizziness, urinating less often than normal, or headache
- a history of seizures
- if you drink alcohol
- recently had coronary artery bypass graft surgery (CABG)
- you are on a low salt diet
- are pregnant. It is not known if VISICOL will harm your unborn baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Any medicine that you take close to the time that you take VISICOL may not work as well. Especially tell your doctor if you take:

- water pills (diuretics)
- medicines for blood pressure or heart problems
- medicines for kidney damage
- medicines for pain, such as aspirin or a non-steroidal anti-inflammatory drug (NSAID)
- a medicines for seizures

- antidepressant medicines or a medicine for anxiety
- a laxative for constipation in the last 7 days. You should not take another medicine that contains sodium phosphate while you take VISICOL.

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines to show your doctor or pharmacist when you get a new prescription.

How should I take VISICOL?

- Take VISICOL exactly as prescribed by your doctor.
- You will take VISICOL on the evening before your colonoscopy and about 12 hours later, on the day of your colonoscopy, as described below.
- **It is important for you to drink clear liquids before, during, and after taking VISICOL. This may help prevent kidney damage.** Examples of **clear liquids** are water, flavored water, lemonade (no pulp), ginger ale, or apple juice. Do not drink any liquids that are colored purple or red.

- **You must read, understand, and follow these instructions to take VISICOL the right way**:

  On the evening before your colonoscopy, you will take a total of 20 VISICOL tablets, as follows:

  1. Take 3 VISICOL tablets with 8 ounces of **clear liquids.**
  2. **Wait 15 minutes.**
  3. Take 3 more VISICOL tablets with 8 ounces of **clear liquids**.
  4. Repeat steps 2 and 3 above four more times. Make sure you wait 15 minutes after each time.
  5. When you take your last dose of VISICOL, the dose will be 2 tablets with 8 ounces of clear liquids.

  On the day of your colonoscopy, you will take another 20 VISICOL Tablets about, 3-5 hours before your colonoscopy, as follows:

  1. Take 3 VISICOL tablets with 8 ounces of **clear liquids.**
  2. **Wait 15 minutes.**
  3. Take 3 more VISICOL tablets with 8 ounces of **clear liquids**.
  4. Repeat steps 2 and 3 above, four more times. Make sure you wait 15 minutes after each time.
  5. When you take your last dose of VISICOL, the dose will be 2 tablets with 8 ounces of clear liquids.

Tell your doctor if you have any of these symptoms while taking VISICOL:

- vomiting, dizziness, or if you urinate less often than normal. These may be signs that you have lost too much fluid while taking VISICOL.
- trouble drinking clear fluids

- severe stomach cramping, bloating, nausea, or headache

If you take too much VISICOL, call your doctor or get medical help right away.

What should I avoid while taking VISICOL?

- You should not take other laxatives or enemas, especially those made with sodium phosphate, while taking VISICOL.
- You should not use VISICOL if you have already used it in the last 7 days.

What are the possible side effects of VISICOL?

VISICOL can cause serious side effects, including:

- See "What is the most important information I should know about VISICOL?"
- seizures or fainting (black-outs). People who take a medicine that contains sodium phosphate, such as VISICOL, can have seizures or faint (become unconscious) even if they have not had seizures before. Tell your doctor right away if you have a seizure or faint while taking VISICOL. See "What should I tell my doctor before taking VISICOL?"
- abnormal heart beat (arrhythmia)
- changes in your blood levels of calcium, phosphate, potassium, sodium

The most common side effects of VISICOL are:

- bloating
- stomach area (abdominal) pain
- nausea
- vomiting

These are not all the possible side effects of VISICOL. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store VISICOL?

- Store VISICOL at room temperature, between 59° F to 86° F (15° C to 30° C).
- Throw away any VISICOL that is not needed.
- **Keep VISICOL and all medicines out of the reach of children.**

General information about VISICOL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VISICOL for a condition for which it was not prescribed. Do not give VISICOL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about VISICOL. If you would like more information about VISICOL, talk with your doctor or pharmacist. You can ask your doctor or pharmacist for information that is written for healthcare professionals. For more information, call 1-866-669-7597 (toll-free) or go to: www.XXXXX.com.

What are the ingredients in VISICOL?

Active ingredients: sodium phosphate monobasic and sodium phosphate dibasic anhydrous

Inactive ingredients: microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide

Salix Pharmaceuticals, Inc.
Morrisville, NC 27560, USA

Revised March 2009

This Medication Guide has been approved by the U.S. Food and Drug Administration.

VENART ###-#/March 2009

OsmoPrep® Tablets

(sodium phosphate monobasic monohydrate, USP,
and sodium phosphate dibasic anhydrous, USP)

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 nonsteriodal anti-inflammatory drugs [NSAIDs]). *See* **WARNINGS**.

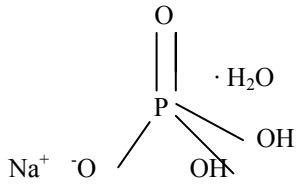
It is important to use the dose and dosing regimen as recommended (pm/am split dose). *See* **DOSAGE and ADMINISTRATION**.

DESCRIPTION

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 oval, white to off-white compressed tablets,debossed with "SLX" on one side of the bisect and "102" on the other side of the bisect. Each OsmoPrep tablet contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic anhydrous, USP for a total of 1.5 grams of sodium phosphate per tablet. Inert ingredients include polyethylene glycol 8000, NF; and magnesium stearate, NF. OsmoPrep is gluten-free.

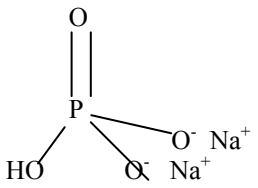
The structural and molecular formulae and molecular weights of the active ingredients are shown below:

- Sodium phosphate monobasic monohydrate, USP



Molecular Formula: $NaH_2PO_4 \cdot H_2O$
Molecular Weight: 137.99

- Sodium phosphate dibasic anhydrous, USP



Molecular Formula: Na_2HPO_4
Molecular Weight: 141.96

OsmoPrep Tablets are for oral administration only.

CLINICAL PHARMACOLOGY

OsmoPrep Tablets, a dosing regimen containing 48 grams of sodium phosphate (32 tablets), induces diarrhea, which effectively cleanses the entire colon. Each administration has a purgative effect for approximately 1 to 3 hours. The primary mode of action is thought to be through the osmotic effect of sodium, causing large amounts of water to be drawn into the colon, promoting evacuation.

Pharmacokinetics

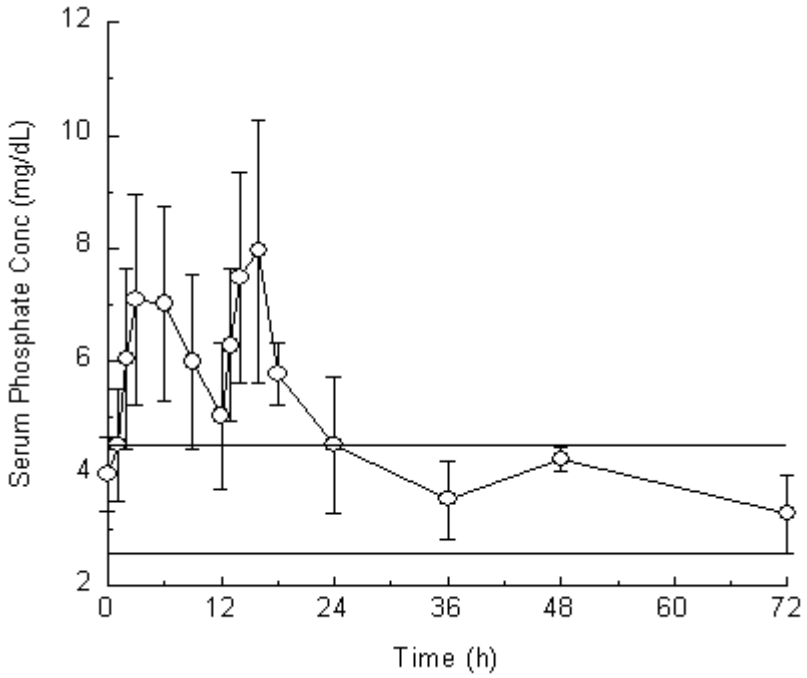
Pharmacokinetic studies with OsmoPrep have not been conducted. However, the following pharmacokinetic study was conducted with Visicol tablets which contain the same active ingredients (sodium phosphate) as OsmoPrep. In addition, Visicol is administered at a dose that is 25% greater than the OsmoPrep dose.

An open-label pharmacokinetic study of Visicol in healthy volunteers was performed to determine the concentration-time profile of serum inorganic phosphorus levels after Visicol administration. All subjects received the approved Visicol dosing regimen (60 grams of sodium phosphate with a total liquid volume of 3.6 quarts) for colon cleansing. A 30 gram dose (20 tablets given as 3 tablets every 15 minutes with 8 ounces of clear liquids) was given beginning at 6 PM in the evening. The 30 gram dose (20 tablets given as 3 tablets every 15 minutes with 8 ounces of clear liquids) was repeated the following morning beginning at 6 AM.

Twenty-three healthy subjects (mean age 57 years old; 57% male and 43% female; and 65% Hispanic, 30% Caucasian, and 4% African-American) participated in this pharmacokinetic study. The serum phosphorus level rose from a mean (± standard deviation) baseline of 4.0 (± 0.7) mg/dL to 7.7 (± 1.6 mg/dL), at a median of 3 hours after the administration of the first 30-gram dose of sodium phosphate tablets (see Figure 1). The serum phosphorus level rose to a mean of 8.4 (± 1.9) mg/dL, at a median of 4 hours after the administration of the second 30-gram dose of sodium phosphate tablets. The serum phosphorus level remained above baseline

for a median of 24 hours after the administration of the initial dose of sodium phosphate tablets (range 16 to 48 hours).

Figure 1. Mean (±standard deviation) serum phosphorus concentrations



The upper (4.5 mg/dL) and lower (2.6 mg/dL) reference limits for serum phosphate are represented by solid bars.

Special Populations

Renal Insufficiency: The effect of renal dysfunction on the pharmacokinetics of OsmoPrep Tablets has not been studied. Since the inorganic form of phosphate in the circulating plasma is excreted almost entirely by the kidneys, patients with renal disease may have difficulty excreting a large phosphate load. Thus, OsmoPrep Tablets should be used with caution in patients with impaired renal function (see WARNINGS).

Hepatic Insufficiency: OsmoPrep Tablets have not been investigated in patients with hepatic failure.

Geriatric: In a single pharmacokinetic study of sodium phosphate tablets, which included 6 elderly volunteers, plasma half-life increased two-fold in subjects > 70 years of age compared to subjects < 50 years of age (3 subjects and 5 subjects, respectively).

Gender: No difference in serum phosphate AUC values were observed in the single pharmacokinetic study conducted with sodium phosphate tablets in 13 male and 10 female healthy volunteers.

CLINICAL STUDIES

The colon cleansing efficacy and safety of OsmoPrep was evaluated in 2 randomized, investigator-blinded, actively controlled, multicenter, U.S. trials in patients scheduled to have an elective colonoscopy. The trials consisted of a dose ranging and a confirmatory phase 3 study.

In the phase 3 trial, patients were randomized into one of the following three sodium phosphate treatment groups: 1) Visicol containing 60 grams of sodium phosphate given in split doses (30 grams in the evening before the colonoscopy and 30 grams on the next day) with at least 3.6 quarts of clear liquids; 2) OsmoPrep containing 60 grams of sodium phosphate given in split doses (30 grams in the evening before the colonoscopy and 30 grams on the next day) with 2.5 quarts of clear liquids; and 3) OsmoPrep containing 48 grams of sodium phosphate (30 grams in the evening before the colonoscopy and 18 grams on the next day) with 2 quarts of clear liquids. Patients were instructed to eat a light breakfast before noon on the day prior to the colonoscopy and then were told to drink only clear liquids after noon on the day prior to the colonoscopy.

The primary efficacy endpoint was the overall colon cleansing response rate in the 4-point Colonic Contents Scale. Response was defined as a rating of "excellent" or "good" on the 4-point scale as determined by the blinded colonoscopist. This phase 3 study was planned to assess the non-inferiority of the two OsmoPrep groups compared to the Visicol group.

The efficacy analysis included 704 adult patients who had an elective colonoscopy. Patients ranged in age from 21 to 89 years old (mean age 56 years old) with 55% female and 45% male patients. Race was distributed as follows: 87% Caucasian, 10% African American, and 3% other race. The OsmoPrep 60 gram and 48 gram treatment groups demonstrated non-inferiority compared to Visicol. See Table 1 for the results.

Table 1: Phase 3 Study – Overall Colon Content Cleansing Response Rates[1]

Treatment Arm (grams of sodium phosphate)	No. of tablets taken at 6 PM on the day prior to colonoscopy	No. of tablets taken the next day[2]	Excellent	Good	Fair	Inadequate	Overall Response Rate (Excellent or Good)
OsmoPrep 32 tabs (48 g) n=236	20	12	76%	19%	3%	2%	95%
OsmoPrep 40 tabs (60 g) n=233	20	20	73%	24%	2%	1%	97%
Visicol 40 tabs (60 g) n=235	20	20	51%	43%	6%	0%	94%

[1] Colon-cleansing efficacy was based on response rate to treatment. A patient was considered to be a responder if overall colon cleansing was rated as "excellent" or "good" on a 4-point scale based on the amount of retained "colonic contents". Excellent was defined as >90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization. Good was defined as >90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization. Fair was defined as >90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed. Inadequate was defined as <90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed.

[2] On the day of the colonoscopy, study medication was taken 3 to 5 hours before the start of the colonoscopy.

Electrolyte Changes

In the OsmoPrep clinical studies, expected serum electrolyte changes (including phosphate, calcium, potassium, and sodium levels) have been observed in patients taking OsmoPrep. In the overwhelming majority of patients, electrolyte abnormalities were not associated with any adverse events.

In the OsmoPrep phase 3 study, 96%, 96%, and 93% of patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep, respectively, developed hyperphosphatemia (defined as phosphate level > 5.1 mg/dL) on the day of the colonoscopy. In this study, patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep had baseline mean phosphate levels of 3.5, 3.5, and 3.6 mg/dL and subsequently developed mean phosphate levels of 7.6, 7.9, and 7.1 mg/dL, respectively, on the day of the colonoscopy.

In the OsmoPrep phase 3 study, 20%, 22%, and 18% of patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep, respectively, developed hypokalemia (defined as a potassium level < 3.4 mEq/L) on the day of the colonoscopy. In this study, patients who took 60 grams of Visicol, 60 grams of OsmoPrep, and 48 grams of OsmoPrep all had baseline potassium levels of about 4.3 mEq/L and then developed a mean potassium level of 3.7 mEq/L on the day of the colonoscopy.

In the OsmoPrep phase 3 trial, several patients on all three sodium phosphate regimens developed hypocalcemia and hypernatremia that did not require treatment.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

OsmoPrep Tablets are contraindicated in patients with biopsy-proven acute phosphate nephropathy.

OsmoPrep Tablets are contraindicated in patients with a known allergy or hypersensitivity to sodium phosphate salts or any of its ingredients.

WARNINGS

Administration of sodium phosphate products prior to colonoscopy for colon cleansing has resulted in fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias. These fatalities have been observed in patients with renal insufficiency, in patients with bowel perforation, and in patients who misused or overdosed sodium phosphate products. It is recommended that patients receiving OsmoPrep be advised to adequately hydrate before, during, and after the use of OsmoPrep.

Considerable caution should be advised before OsmoPrep Tablets are used in patients with the following illnesses: severe renal insufficiency (creatinine clearance less than 30 mL/minute), congestive heart failure, ascites, unstable angina, gastric retention, ileus, acute bowel obstruction, pseudo-obstruction of the bowel, severe chronic constipation, bowel perforation, acute colitis, toxic megacolon, gastric bypass or stapling surgery, or hypomotility syndrome.

Consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in patients who may be at increased risk for serious adverse events, including those with history of renal insufficiency, history of ─ or at greater risk of ─ acute phosphate nephropathy, known or suspected electrolyte disorders, seizures, arrhythmias, cardiomyopathy, prolonged QT, recent history of a MI and those with known or suspected hyperphosphatemia, hypocalcemia, hypokalemia, and hypernatremia. Also if patients develop vomiting and/or signs of dehydration then measure post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN).

Renal Disease, Acute Phosphate Nephropathy, and Electrolyte Disorders
There have been rare, but serious, reports of renal failure, acute phosphate nephropathy, and nephrocalcinosis in patients who received oral sodium phosphate products (including oral sodium phosphate solutions and tablets) for colon cleansing prior to colonoscopy. These cases often resulted in permanent impairment of renal function and several patients required long-term dialysis. The time to onset is typically within days; however, in some cases, the diagnosis of these events has been delayed up to several months after the ingestion of these products. Patients at increased risk of acute phosphate nephropathy may include patients with the following: hypovolemia, baseline kidney disease, increased age, and patients using medicines that affect renal perfusion or function [such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs).

Use OsmoPrep with caution in patients with impaired renal function, patients with a history of acute phosphate nephropathy, known or suspected electrolyte disturbances (such as dehydration), or people taking concomitant medications that may affect electrolyte levels (such as diuretics). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have their electrolytes corrected before treatment with OsmoPrep Tablets.

Seizures
There have been rare reports of generalized tonic-clonic seizures and/or loss of consciousness associated with use of sodium phosphate products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia) and low serum osmolality. The neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities. OsmoPrep should be used with caution in patients with a history of seizures and in patients at higher risk of seizure [patients using concomitant medications that lower the seizure threshold (such as tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, or patients with known or suspected hyponatremia].

Cardiac Arrhythmias

There have been rare, but serious, reports of arrhythmias associated with the use of sodium phosphate products. OsmoPrep should be used with caution in patients with higher risk of arrhythmias (patients with a history of cardiomyopathy, patients with prolonged QT, patients with a history of uncontrolled arrhythmias, and patients with a recent history of a myocardial infarction). Pre-dose and post-colonoscopy ECGs should be considered in patients with high risk of serious, cardiac arrhythmias.

PRECAUTIONS

General

Patients should be instructed to drink 8 ounces of clear liquids with each 4-tablet dose of OsmoPrep Tablets. Patients should take a total of 2 quarts of clear liquids with OsmoPrep. Inadequate fluid intake, as with any effective purgative, may lead to excessive fluid loss, hypovolemia, and dehydration. Dehydration from purgation may be exacerbated by inadequate oral fluid intake, vomiting, and/or use of diuretics.

Patients should be instructed not to administer additional laxative or purgative agents, particularly additional sodium phosphate-based purgative or enema products.

Prolongation of the QT interval has been observed in some patients who were dosed with sodium phosphate colon preparations. QT prolongation with sodium phosphate tablets has been associated with electrolyte imbalances, such as hypokalemia and hypocalcemia. OsmoPrep Tablets should be used with caution in patients who are taking medications known to prolong the QT interval, since serious complications may occur. Pre-dose and post-colonoscopy ECGs should be considered in patients with known prolonged QT.

Administration of OsmoPrep Tablets may induce colonic mucosal aphthous ulcerations, since this endoscopic finding was observed with other sodium phosphate cathartic preparations. In the OsmoPrep clinical program, aphthous ulcers were observed in 3% of patients who took the 48 gram OsmoPrep dosing regimen. This colonoscopic finding should be considered in patients with known or suspected inflammatory bowel disease.

Because published data suggest that sodium phosphate absorption may be enhanced in patients experiencing an acute exacerbation of chronic inflammatory bowel disease, OsmoPrep Tablets should be used with caution in such patients.

Drug Interactions

Medications administered in close proximity to OsmoPrep Tablets may not be absorbed from the gastrointestinal tract due to the rapid intestinal peristalsis and watery diarrhea induced by the purgative agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of OsmoPrep. Studies to evaluate the effect of OsmoPrep on fertility or its mutagenic potential have not been performed.

Pregnancy. Teratogenic Effects: Pregnancy Category C.

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

Pediatric Use

The safety and efficacy of OsmoPrep Tablets have not been demonstrated in patients less than 18 years of age.

Geriatric Use

In controlled colon preparation trials of OsmoPrep, 228 (24%) of 931 patients were 65 years of age or older. In addition, 49 (5%) of the 931 patients were 75 years of age or older.

Of the 228 geriatric patients in the trials, 134 patients (59%) received at least 48 grams of OsmoPrep. Of the 49 patients 75 years old or older in the trials, 27 (55%) patients received at least 48 grams of OsmoPrep. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients. However, the mean phosphate levels in geriatric patients were greater than the phosphate levels in younger patients after OsmoPrep administration. The mean colonoscopy-day phosphate levels in patients 18-64, 65-74, and ≥ 75 years old who received 48 grams of OsmoPrep in the phase 3 study were 7.0, 7.3, and 8.0 mg/dL, respectively. In addition, in all three sodium phosphate treatment groups, the mean phosphate levels in patients 18-64, 65-74, and ≥ 75 years old in the phase 3 study were 7.4, 7.9, and 8.0 mg/dL, respectively, after sodium phosphate administration. Greater sensitivity of some older individuals cannot be ruled out; therefore, OsmoPrep Tablets should be used with caution in geriatric patients.

Sodium phosphate is known to be substantially excreted by the kidney, and the risk of adverse reactions with sodium phosphate may be greater in patients with impaired renal function. Since geriatric patients are more likely to have impaired renal function, consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in these patients (see WARNINGS). It is recommended that patients receiving OsmoPrep be advised to adequately hydrate before, during, and after the use of OsmoPrep.

ADVERSE REACTIONS

Abdominal bloating, abdominal pain, nausea, and vomiting were the most common adverse events reported with the use of OsmoPrep Tablets. Dizziness and headache were reported less frequently. Since diarrhea was considered as a part of the efficacy of OsmoPrep, diarrhea was not defined as an adverse event in the clinical studies. Table 2 shows the most common adverse

events associated with the use of 48 grams of OsmoPrep, 60 grams of OsmoPrep, and 60 grams of Visicol in the colon preparation trials (n= 931).

Table 2: Frequency of Adverse Events of Any Severity Occurring in Greater Than 3% of Patients in the OsmoPrep Trials

	OsmoPrep 32 tabs (48 g) N=272	**OsmoPrep 40 tabs (60 g) N=265**	**Visicol 40 tabs (60 g) N=268**
Bloating	31%	39%	41%
Nausea	26%	37%	30%
Abdominal Pain	23%	24%	25%
Vomiting	4%	10%	9%

Postmarketing Experience

In addition to adverse events reported from clinical trials, the following adverse events have been identified during post-approval use of OsmoPrep. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to OsmoPrep, or a combination of these factors.

General: Hypersensitivity reactions including anaphylaxis, rash, pruritus, urticaria, throat tightness, bronchospasm, dyspnea, pharyngeal edema, dysphagia, paresthesia and swelling of the lips and tongue, and facial swelling.

Cardiovascular: Arrhythmias

Nervous system: Seizures

Renal: Renal impairment, increased blood urea nitrogen (BUN), increased creatinine, acute renal failure, acute phosphate nephropathy, nephrocalcinosis, and renal tubular necrosis.

DRUG ABUSE AND DEPENDENCE

Laxatives and purgatives (including OsmoPrep) have the potential for abuse by bulimia nervosa patients who frequently have binge eating and vomiting.

OVERDOSAGE

There have been no reported cases of overdosage with OsmoPrep Tablets. Purposeful or accidental ingestion of more than the recommended dosage of OsmoPrep Tablets might be expected to lead to severe electrolyte disturbances, including hyperphosphatemia, hypocalcemia, hypernatremia, or hypokalemia, as well as dehydration and hypovolemia, with attendant signs and symptoms of these disturbances. Certain severe electrolyte disturbances resulting from overdose may lead to cardiac arrhythmias, seizure, renal failure, and death. The patient who has taken an overdosage should be monitored carefully, and treated symptomatically for complications until stable.

DOSAGE AND ADMINISTRATION

The recommended dose of OsmoPrep Tablets for colon cleansing for adult patients is 32 tablets (48 grams of sodium phosphate) taken orally with a total of 2 quarts of clear liquids in the following manner:

The evening before the colonoscopy procedure: 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 procedure: Starting 3-5 hours before the procedure, take 4 OsmoPrep Tablets with 8 ounces of clear liquids every 15 minutes for a total of 12 tablets.

Patients should be advised of the importance of taking the recommended fluid regimen. It is recommended that patients receiving OsmoPrep be advised to adequately hydrate before, during, and after the use of OsmoPrep.

Patients should not use OsmoPrep for colon cleansing within seven days of previous administration. No additional enema or laxative is required, and patients should be advised NOT to take additional agents, particularly those containing sodium phosphate.

HOW SUPPLIED

OsmoPrep Tablets are supplied in child-resistant bottles containing 100 tablets. Each tablet contains 1.102 g sodium phosphate monobasic monohydrate, USP and 0.398 g sodium phosphate dibasic anhydrous, USP for a total of 1.5 g of sodium phosphate per tablet.

Each bottle contains two silica desiccant packets, which should not be ingested.

NDC 65649-701-41 (100 tablet bottle)

Rx only.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Discard any unused portion.

Manufactured by:
WellSpring Pharmaceutical Canada Corp.

Oakville, Ontario Canada L6H 1M5
for:
Salix Pharmaceuticals, Inc.
Morrisville, NC 27560
Made in Canada
VENART ###.#/Jan. 2009

Product protected by US Patent No. 5,616,346 and other pending applications.

Medication Guide

OsmoPrep® (AhZ-MŌ-prĕp)

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

Read the Medication Guide that comes with OsmoPrep before you take it and each time you take it. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about OsmoPrep, ask your doctor or pharmacist.

What is the most important information I should know about OsmoPrep?

OsmoPrep can cause serious side effects, including:

Serious kidney problems. Rare, but serious kidney problems can happen in people who take medicines made with sodium phosphate, including OsmoPrep, to clean your colon before a colonoscopy. These kidney problems can sometimes lead to kidney failure or the need for dialysis for a long time. These problems often happen within a few days, but sometimes may happen several months after taking OsmoPrep.

Conditions that can make you more at risk for having serious kidney problems with OsmoPrep include if you:

- lose too much body fluid (dehydration)
- have slow moving bowels
- have bowels blocked with stool (constipation)
- have severe stomach pain or bloating
- have any disease that causes bowel irritation (colitis)
- have kidney disease
- have heart failure
- take water pills or non-steroidal anti-inflammatory drugs (NSAIDS).

Your age may also affect your risk for having kidney problems with OsmoPrep.

Before you start taking OsmoPrep, tell your doctor if you:

- have kidney problems
- take any medicines for blood pressure, heart disease, or kidney disease.

Severe fluid loss. People who take medicines that contain sodium phosphate can have severe loss of body fluid, with severe changes in body salts in the blood, and abnormal heart rhythms. These problems can lead to death.

Tell your doctor if you have any of these symptoms of loss of too much body fluid (dehydration) while taking OsmoPrep:

- vomiting
- dizziness
- urinating less often than normal
- headache

See "What are the possible side effects of OsmoPrep?" for more information about side effects.

What is OsmoPrep?

OsmoPrep is a prescription medicine used in adults 18 years and older, to clean your colon before a colonoscopy. OsmoPrep cleans your colon by causing you to have diarrhea. Cleaning your colon helps your doctor see the inside of your colon more clearly during the colonoscopy.

It is not known if OsmoPrep is safe and works in children under age 18.

Who should not take OsmoPrep?

Do not take OsmoPrep if:

- you have had a kidney biopsy that shows you have kidney problems because of too much phosphate
- you are allergic to sodium phosphate salts or any of the ingredients in OsmoPrep. See the end of this Medication Guide for a list of ingredients in OsmoPrep.

What should I tell my doctor before taking OsmoPrep?

Before taking OsmoPrep, tell your doctor about all your medical conditions, including if you have:

- any of the medical conditions listed in the section "What is the most important information I should know about OsmoPrep?"
- irritation of the bowel (colitis). OsmoPrep can cause symptoms of irritable bowel disease to flare-up.
- damage to your bowels
- problems with abnormal heart beat
- had a recent heart attack or have other heart problems
- symptoms of too much body fluid loss (dehydration) including vomiting, dizziness, urinating less often than normal, or headache
- had stomach surgery
- a history of seizures
- if you drink alcohol
- are on a low salt diet
- are pregnant. It is not known if OsmoPrep will harm your unborn baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Any medicine that you take close to the time that you take OsmoPrep may not work as well. Especially tell your doctor if you take:

- water pills (diuretics)
- medicines for blood pressure or heart problems.
- medicines for kidney damage
- medicines for pain, such as aspirin or a non-steroidal anti-inflammatory drug (NSAID)
- a medicine for seizures

- a laxative for constipation in the last 7 days. You should not take another medicine that contains sodium phosphate while you take OsmoPrep.

Ask your doctor if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of your medicines to show your doctor or pharmacist when you get a new prescription.

How should I take OsmoPrep?

- Take OsmoPrep exactly as prescribed by your doctor.
- **It is important for you to drink clear liquids before, during, and after taking OsmoPrep. This may help prevent kidney damage.** Examples of **clear liquids** are water, flavored water, lemonade (no pulp), ginger ale, or apple juice. Do not drink any liquids colored purple or red.

You must read, understand, and follow these instructions to take OsmoPrep the right way:

On the evening before your colonoscopy, you will take a total of 20 OsmoPrep tablets, as follows:

1. Take 4 OsmoPrep tablets with 8 ounces of **clear liquids**.
2. **Wait 15 minutes**.
3. Take 4 more OsmoPrep tablets 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.

On the day of your colonoscopy you will take a total of 12 OsmoPrep tablets, starting about 3 to 5 hours before your colonoscopy, as follows:

1. Take 4 OsmoPrep tablets with 8 ounces of **clear liquids.**
2. **Wait 15 minutes.**
3. Take 4 more OsmoPrep tablets with 8 ounces of **clear liquids**.
4. Repeat steps 2 and 3 one more time.

Tell your doctor if you have any of these symptoms while taking OsmoPrep:

- vomiting, dizziness, or if you urinate less often than normal. These may be signs that you have lost too much fluid while taking OsmoPrep.
- trouble drinking clear fluids
- severe stomach cramping, bloating, nausea, or headache

If you take too much OsmoPrep, call your doctor or get medical help right away.

What should I avoid while taking OsmoPrep?

- You should not take other laxatives or enemas made with sodium phosphate, while taking OsmoPrep.

- You should not use OsmoPrep if you have already used it in the last 7 days.

What are the possible side effects of OsmoPrep?

OsmoPrep can cause serious side effects, including:

- See "What is the most important information I should know about OsmoPrep?"
- Seizures or fainting (black-outs). People who take a medicine that contains sodium phosphate, such as OsmoPrep, can have seizures or faint (become unconscious) even if they have not had seizures before. Tell your doctor right away if you have a seizure or faint while taking OsmoPrep.
- abnormal heart beat (arrhythmias)
- changes in your blood levels of calcium, phosphate, potassium, sodium

The most common side effects of OsmoPrep are:

- bloating
- stomach area (abdominal) pain
- nausea
- vomiting

These are not all the possible side effects of OsmoPrep. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store OsmoPrep?

- Store OsmoPrep at room temperature, between 59° F to 86° F (15° C to 30° C).
- Throw away any OsmoPrep that is not needed.
- **Keep OsmoPrep and all medicines out of the reach of children.**

General information about OsmoPrep

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OsmoPrep for a condition for which it was not prescribed. Do not give OsmoPrep to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about OsmoPrep. If you would like more information about OsmoPrep, talk with your doctor or pharmacist. You can ask your doctor or pharmacist for information that is written for healthcare professionals. For more information, call 1-866-669-7597 (toll-free) or go to www.XXXXX.com.

What are the ingredients in OsmoPrep?

Active ingredients: sodium phosphate monobasic and sodium phosphate dibasic anhydrous

Inactive ingredients: polyethylene glycol 8000 and magnesium stearate

Revised March 2009

Salix Pharmaceuticals, Inc.
Morrisville, NC 27560, USA

This Medication Guide has been approved by the U.S. Food and Drug Administration.

VENART ###-#/March 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-013

NDA 21-892/S-003

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.

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/s/

Christopher L Leptak
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MEDICAL OFFICER

Joyce Korvick
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	Prior Approval Supplement Safety Labeling Changes under 505(0)(4)
Application Number(s)	NDA 21-097/S-013
Priority or Standard	Standard
Submit Date(s)	January 8, 2009
Received Date(s)	January 9, 2009
PDUFA Goal Date	February 6, 2009
Reviewer Name(s)	Erica L. Wynn, MD MPH
Review Completion Date	January 16, 2008
Established Name	Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP
Trade Name	Visicol
Therapeutic Class	Purgative
Applicant	Salix Pharmaceuticals, Inc.
Formulation(s)	Tablets
Dosing Regimen	1.5 grams of sodium phosphate per tablet (total of 60 grams given in two doses of 30 grams

	approximately 12 hours apart)
Indication(s)	Bowel Cleansing Preparation Prior to Colonoscopy
Intended Population(s)	Patients undergoing annual screening and /or diagnostic colonoscopy

Erica Wynn
NDA 21-097
NDA 21-892
Visicol and OsmoPrep

1. Recommendations

1.1 Recommendation on Regulatory Action

In a prior correspondence the sponsor, Salix Pharmaceuticals Inc., was notified of the need to make safety related changes to the labels for Visicol and OsmoPrep in accordance with section 505(o)(4), of the FDCA. This decision was based upon review of "new safety information" as defined in FDAAA. The Prior Approval Supplement (PAS) which the sponsor submitted on January 8, 2009, has been received and reviewed. Safety labels were compared with the original safety labels for Visicol and OsmoPrea as they were approved on 3/16/2006 and 3/31/2006 respectively. It is the recommendation of this Reviewer that the prior approval labeling supplement be approved with a few minor modifications as delineated in Section 3. (Please note that additions are noted by yellow underline and deletions are noted by yellow ~~strikethrough~~). It is also important to note that additional consultations from the Division of Drug, Marketing, Advertising, and Communications (DDMAC) and the Division of Risk Management (DRISK) are still pending. Amendments to the current label review may be required when additional information becomes available.

2 Introduction and Regulatory Background

2.1 Product Information

Visicol and OsmoPrep are purgatives used to clean the colon prior to colonoscopy. Both contain the same active ingredients (sodium phosphate). Visicol contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic anhydrous, USP for a total of 1.5 grams of sodium phosphate per tablet. OsmoPrep also contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic anhydrous, USP for a total of 1.5 grams of sodium phosphate per tablet. However, OsmoPrep also contains polyethylene glycol 8000, NF and magnesium stearate, NF; is manufactured with a highly soluble tablet binder; and does not contain microcrystalline cellulose. The purgative effect of both medications is approximately 1 to 3 hours. Visicol is administered in two doses of 30 grams given approximately 12 hours apart (total of 60 grams of sodium phosphate). The dosing regimen for OsmoPrep contains approximately 48 grams of sodium phosphate and is also divided into two doses. The primary mode of action is thought to be through the osmotic effect of sodium causing large amounts of water to be drawn into the colon producing bowel evacuation.

2.2 Important Safety Issues With Consideration to Related Drugs

Since Visicol and OsmoPrep were approved on September 21, 2000, and March 16, 2006, respectively, the FDA has received new information regarding the risk of acute

phosphate nephropathy (a type of acute kidney) injury associated with the use of oral sodium phosphate products. In some reports, patients have developed permanent impairment of renal function and some have required long-term dialysis. While some cases have occurred in patients without identifiable risk factors, patients at increased risk may include those with increased age (over 55 years), hypovolemia, increased bowel transit time), active colitis, baseline kidney disease, or those using medicines that affect renal perfusion or function.

2.3 Summary of Presubmission Regulatory Activity Related to Submission

In March 2006, information regarding the risk of acute phosphate nephropathy associated with the use of oral sodium phosphate products for bowel cleansing was added to the **Warnings** section of the existing label for Visicol and incorporated into the label with which OsmoPrep was approved on March 16, 2006. Two months later (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. Subsequently, the FDA continued to receive reports of acute kidney injury with both prescription and over-the-counter oral sodium phosphate products. In December of 2008, Salix Pharmaceuticals, Inc. was notified (by letter) of the need to make safety related changes to the labeling for Visicol and OsmoPrep in accordance with section 505(o)(4), of the FDCA and to create a Medication Guide to inform patients of the possibility of serious side effects associated with the drugs. Additionally the FDA determined that a REMS (Risk Evaluation and Mitigation Strategy) for each drug was necessary to ensure that the benefits of the drugs outweighed the risks. This decision was based upon review of "new safety information" as defined in FDAAA. Components of the REMS included a: 1) Medication Guide 2) Communication Plan to healthcare providers and 3) Timetable for assessment of the REMS. Additionally Salix is required to conduct 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. Subsequent to the letter, Salix had a teleconference call with the FDA in January of 2009 to discuss proposed labeling changes and the drafts of the Medication Guides.

3. Labeling Modifications

In the submission received on January 9, 2008, the requested labeling changed, as delineated during the teleconference on January 5, 2009, were made. It is recommended that the prior approval labeling supplement be approved with the following additional minor modifications:

Erica Wynn
NDA 21-097
NDA 21-892
Visicol and OsmoPrep

1. During the teleconference both the FDA and Salix agreed to the replacement of patients at increased risk of acute phosphate nephropathy may include those with (b) (4) with (b) (4) This is found within the BOXED WARNINGS sections of both the label for Visicol and OsmoPrep. The most recently submitted drafts for both product labels states that there is an increased risk of acute phosphate nephropathy with *"increased age."* On January 28, 2009, an inter-divisional meeting was held with DGP, DRISK, and OSE to discuss this and it was decided that the label as currently submitted is more appropriate and acceptable.

2. Within the BOXED WARNINGS of the labels for both Visicol and OsmoPrep, the reference made to Dosage and Administration section is acceptable as written.

3. On page 1 of the Visicol label, under the DESCRIPTION, there is a redundancy and the words (b) (4) should be omitted. The sentence should correctly state that "Each tablet contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic, anhydrous, USP for a total of 1.5 grams of sodium phosphate per tablet."

4. On page 5 of the Visicol label and page 6 of the OsmoPrep label respectively, under the section WARNINGS… RENAL DISEASE, ACUTE PHOSPHATE NEPHROPATHY, AND ELECTROLYTE DISORDERS, the proposed changes are acceptable. However the grammar was corrected so the sentence reads as follows: "…serious reports of renal failure, acute phosphate nephropathy, and nephrocalcinosis in patients who received oral sodium phosphate products. .."

5. On page 8 of the Visicol label, under POST MARKETING EXPERIENCE, we agree with the proposed changes. However the label should state "the following adverse events have been identified during post-approval use of *Visico*l" rather than OsmoPrep. Likewise the label should also state that "frequency of reporting or causal connection to *Visicol*" rather than OsmoPrep.

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/s/

Erica Wynn
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MEDICAL OFFICER

Joyce Korvick
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MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-097/S-013
NDA 21-892/S-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-097/S-013
NDA 21-892/S-003

PRIOR APPROVAL SUPPLEMENT

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

Dear Ms. Glifort:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Products:	Visicol (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets, and OsmoPrep (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets
NDA/Supplement Numbers:	21-097/S-013 21-892/S-003
Date of supplements:	January 8, 2009
Date of receipt:	January 9, 2009

On December 10, 2008, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Visicol and OsmoPrep to address the risk of acute kidney injury associated with the use of these products based on new safety information about this risk identified since the product was approved. You were directed to submit a prior-approval supplement proposing changes to the approved labeling 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.

On January 9, 2009, FDA received your prior-approval supplement that contained your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for these supplements, NDA 21-097/S-013 and NDA 21-892/S-003, ends on March 10, 2009.

If you have 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

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/s/

Joyce Korvick

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Wayne Amchin, RPM, DDMAC			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Matthew Scherer, RPM, Division of Gastroenterology Products, 301-796-2307	
DATE 1-28-09	IND NO.	NDA NO. 21-892 21-097	TYPE OF DOCUMENT label, med guide and REMS submissions	DATE OF DOCUMENT Initial submissions: 1-8-09
NAME OF DRUG OsmoPrep and Visicol	PRIORITY CONSIDERATION high		CLASSIFICATION OF DRUG cathartic/laxative	DESIRED COMPLETION DATE 2-6-09 or PI and MG review

NAME OF FIRM:

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: The Division of Gastroenterology Products requests DDMAC's assistance in reviewing Salix's submissions in response to our supplement request letter dated 12-10-09. The first set of submissions, revised Package Inserts and Medication Guides were received on January 9, 2009. We are further expecting REMS submissions to these NDAs on or before February 8, 2009. I will deliver the Supplement Request Letter and copies of the submissions if needed. Please contact myself, Erica Wynn, Medical Officer (6-4856), Joyce Korvick, Safety Deputy Director (6-0936) or Ruyi He, Acting Deputy Director if you have any questions.

SIGNATURE OF REQUESTOR Matthew Scherer	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Matthew Scherer
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