

Visicol[®] and OsmoPrep[®]
Supplement – Proposed REMS

NDA 21-097 and 21-892
Amendment

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 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

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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.

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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.



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]).

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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

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



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](#)

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

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/s/

JOYCE A KORVICK
10/13/2009