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 white to off-white compressed tablets. 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, US 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.

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

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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 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 and acute phosphate nephropathy (also known as

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. 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 (eg, 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, pharyngeal edema, paresthesia and swelling of the lips, and facial swelling.

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 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:

WellSpring Pharmaceutical Canada Corp.
Oakville, Ontario Canada L6H 1M5

for:

Salix Pharmaceuticals, Inc.
Morrisville, NC 27560
Made in Canada

6630.00