HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUPREP Bowel Prep Kit safely and effectively. See full prescribing information for SUPREP Bowel Prep Kit

SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution

Initial U.S. Approval: 08/2010

----------INDICATIONS AND USAGE----------

SUPREP Bowel Prep Kit is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults (1)

----------DOSAGE AND ADMINISTRATION----------

Dilute the solution prior to use. See FULL PRESCRIBING INFORMATION for complete dosing and administration instructions (2)

Split Dose (2-Day) Regimen

- Evening before colonoscopy: dilute one bottle with water to a total volume of 16 oz. (up to the fill line) and drink the entire amount.
- Drink 32 ounces of water over the next hour.
- Next morning: repeat both steps using the second bottle.
- Complete preparation at least 2 hours before colonoscopy or as directed by physician.

----------DOSAGE FORMS AND STRENGTHS----------

- Two 6 ounce bottles of oral solution, each containing sodium sulfate 17.5 grams, potassium sulfate 3.13 grams, and magnesium sulfate 1.6 grams. (3)

----------CONTRAINDICATIONS----------

- Gastrointestinal obstruction (4, 5.6)
- Bowel perforation (4, 5.6)
- Gastric retention (4)
- Ileus (4)
- Toxic colitis or toxic megacolon (4)
- Known allergies to components of the kit (4, 11)

----------WARNINGS AND PRECAUTIONS----------

- Risk of fluid and electrolyte abnormalities, arrhythmias, seizures and renal impairment– assess concurrent medications and consider testing in some patients (5.1, 5.2, 5.3)
- Patients with renal insufficiency– use caution, ensure adequate hydration and consider testing (5.4)
- Suspected GI obstruction or perforation – rule out the diagnosis before administration (4, 5.6)
- Patients at risk for aspiration – observe during administration (5.7)
- Not for direct ingestion – dilute and take with additional water (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥3%) are: overall discomfort, abdominal fullness, nausea, abdominal cramping, and vomiting (6)

To report SUSPECTED ADVERSE REACTIONS, contact Braintree Laboratories, Inc. at 1-800-874-6756 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Some drugs increase risks due to fluid and electrolyte changes (7.1)
- Oral medication taken within 1 hour of start of each dose might not be absorbed properly (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised 11/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUPREP Bowel Prep Kit is indicated for cleansing of the colon as a preparation for colonoscopy in adults.

2 DOSAGE AND ADMINISTRATION

SUPREP Bowel Prep Kit should be taken as a split-dose oral regimen.

The dose for colon cleansing requires administration of two bottles of SUPREP Bowel Prep Kit. Each bottle is administered as 16 ounces of diluted SUPREP solution with an additional 1 quart of water taken orally. The total volume of liquid required for colon cleansing (using two bottles) is 3 quarts (approximately 2.8 L) taken orally prior to the colonoscopy in the following way:

Split-Dose (Two-Day) Regimen

Day prior to colonoscopy:

- A light breakfast may be consumed, or have only clear liquids on the day before colonoscopy. Avoid red and purple liquids, milk, and alcoholic beverages.
- Early in the evening prior to colonoscopy: pour the contents of one bottle of SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount.
- Drink two additional containers filled to the 16 ounce line with water over the next hour.

Day of colonoscopy:

- Have only clear liquids until after the colonoscopy. Avoid red and purple liquids, milk, and alcoholic beverages.
- The morning of colonoscopy (10 to 12 hours after the evening dose): pour the contents of the second bottle of SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount.
- Drink two additional containers filled to the 16 ounce line with water over the next hour.
- Complete all SUPREP Bowel Prep Kit and required water at least two hours prior to colonoscopy or as directed by physician.

3 DOSAGE FORMS AND STRENGTHS

Two 6 ounce bottles of oral solution.

Each 6 ounce bottle contains: sodium sulfate 17.5 grams, potassium sulfate 3.13 grams, magnesium sulfate 1.6 grams.

4 CONTRAINDICATIONS

- Gastrointestinal obstruction
- Bowel perforation
- Gastric retention
- Ileus
- Toxic colitis or toxic megacolon
- Known allergies to components of the kit [*see Description (11)*]

5 WARNINGS AND PRECAUTIONS

5.1 Serious Fluid and Serum Chemistry Abnormalities

Advise all patients to hydrate adequately before, during, and after the use of SUPREP Bowel Prep Kit. If a patient develops significant vomiting or signs of dehydration after taking SUPREP Bowel Prep Kit, consider performing post-colonoscopy lab tests (electrolytes, creatinine, and BUN). Fluid and electrolyte disturbances can lead to serious adverse events including cardiac arrhythmias, seizures and renal impairment.

Patients with electrolyte abnormalities should have them corrected before treatment with SUPREP Bowel Prep Kit. In addition, use caution when prescribing SUPREP Bowel Prep Kit for patients with conditions, or who are using medications, that increase the risk for fluid and electrolyte disturbances or may increase the risk of adverse events of seizure, arrhythmias, and renal impairment. [*see Drug Interactions* (7.1)]

SUPREP Bowel Prep Kit can cause temporary elevations in uric acid. [*see Adverse Reactions* (6.1)]. Uric acid fluctuations in patients with gout may precipitate an acute flare. The potential for uric acid elevation should be considered before administering SUPREP Bowel Prep Kit to patients with gout or other disorders of uric acid metabolism.

5.2 Cardiac Arrhythmias

There have been rare reports of serious arrhythmias associated with the use of ionic osmotic laxative products for bowel preparation. Use caution when prescribing SUPREP Bowel Prep Kit for patients at increased risk of arrhythmias (e.g., patients with a history of prolonged QT, uncontrolled arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy). Pre-dose and post-colonoscopy ECGs should be considered in patients at increased risk of serious cardiac arrhythmias.

5.3 Seizures

There have been reports of generalized tonic-clonic seizures and/or loss of consciousness associated with use of bowel preparation 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.

Use caution when prescribing SUPREP Bowel Prep Kit for patients with a history of seizures and in patients at increased risk of seizure, such as patients taking medications that lower the seizure threshold (e.g., tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, or patients with known or suspected hyponatremia.

5.4 Renal Impairment

Use caution when prescribing SUPREP Bowel Prep Kit for patients with impaired renal function or patients taking concomitant medications that may affect renal function (such as diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or non-steroidal anti-inflammatory drugs). Advise these patients of the importance of adequate hydration, and consider performing baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in these patients.

5.5 Colonic Mucosal Ulcerations and Ischemic Colitis

Administration of osmotic laxative products may produce colonic mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Concurrent use of stimulant laxatives and SUPREP Bowel Prep Kit may increase these risks. The potential for mucosal ulcerations resulting from the bowel preparation should be considered when interpreting colonoscopy findings in patients with known or suspect inflammatory bowel disease (IBD).

5.6 Use in Patients with Significant Gastrointestinal Disease

If gastrointestinal obstruction or perforation is suspected, perform appropriate diagnostic studies to rule out these conditions before administering SUPREP Bowel Prep Kit.

Use with caution in patients with severe active ulcerative colitis.

5.7 Aspiration

Use with caution in patients with impaired gag reflex and patients prone to regurgitation or aspiration. Such patients should be observed during administration of SUPREP Bowel Prep Kit solution.

5.8 Not for Direct Ingestion

Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance. Direct ingestion of the undiluted solution may increase the risk of nausea, vomiting, dehydration, and electrolyte disturbances.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in clinical studies of another drug and may not reflect the rates observed in practice.

In a multicenter, controlled clinical trial comparing SUPREP Bowel Prep Kit with a bowel prep containing polyethylene glycol and electrolytes (PEG + E) that were administered in

a split-dose (2-day) regimen, the most common adverse reactions after administration of SUPREP Bowel Prep Kit were overall discomfort, abdominal distention, abdominal pain, nausea, vomiting, and headache; see Table 1, below. Less common Adverse Reactions occurring were AV Block (1 case) and CK increase. In this study, patients receiving SUPREP Bowel Prep Kit were limited to a light breakfast followed by clear liquids; patients receiving the PEG + E bowel prep were allowed to have a normal breakfast and a light lunch, followed by clear liquids.

Table 1: Treatment-Emergent Adverse Reactions Observed in at Least 2% of Patients on the Split-Dose (2-Day) Regimen

Symptom	Split-Dose (2-Day) Regimen	
	SUPREP N=190	PEG + E product N=189
Overall Discomfort	54 %	67%
Abdominal Distension	40%	52%
Abdominal Pain	36%	43%
Nausea	36%	33%
Vomiting	8%	4%
Headache	1.1 %	0.5%

Table 2 shows the percentages of patients who developed new abnormalities of important electrolytes and uric acid after completing the bowel preparation with either SUPREP Bowel Prep Kit or PEG+E administered as a split-dose (2-day) regimen.

Table 2: Patients with Normal Baseline Serum Chemistry with A Shift to an Abnormal Value While on the Split-Dose (2-Day) Regimen

		Day of Colonoscopy n (%)*	Day 30 n (%)*
Anion gap (high) †	SUPREP	14 (8.9)	3 (1.9)
	PEG + Electrolytes	12 (7.6)	2 (1.4)
Bicarbonate (low)	SUPREP	20 (12.7)	7 (4.4)
	PEG + Electrolytes	24 (15.2)	4 (2.7)
Bilirubin, total (high)	SUPREP	14 (8.5)	0 (0)
	PEG + Electrolytes	20 (11.7)	3 (1.9)
BUN (high)	SUPREP	2 (1.6)	14 (11.2)
	PEG + Electrolytes	4 (2.9)	19 (14.5)
Calcium (high)	SUPREP	16 (10.4)	8 (5.2)
	PEG + Electrolytes	6 (3.7)	6 (3.9)
Chloride (high)	SUPREP	4 (2.4)	6 (3.7)
	PEG + Electrolytes	20 (12.2)	6 (3.8)

Creatinine (high)	SUPREP	3 (1.9)	5 (3.2)
	PEG + Electrolytes	2 (1.2)	8 (5.2)
Osmolality (high)	SUPREP	8 (5.8)	NA
	PEG + Electrolytes	19 (12.9)	NA
Osmolality (low)	SUPREP	3 (2.2)	NA
	PEG + Electrolytes	2 (1.4)	NA
Potassium (high)	SUPREP	3 (1.8)	6 (3.7)
	PEG + Electrolytes	5 (2.9)	8 (4.9)
Sodium (low)	SUPREP	5 (3.1)	1 (0.6)
	PEG + Electrolytes	4 (2.3)	2 (1.2)
Uric acid (high)	SUPREP	27 (23.5)	13 (11.5)
	PEG + Electrolytes	12 (9.5)	20 (16.7)

*Percent (n/N) of patients where N=number of patients with normal baseline who had abnormal values at the timepoint(s) of interest.

†Patients with normal bicarbonate at baseline who developed low bicarbonate (≤ 21 mEq/L) and high anion gap (≥ 13 mEq/L) on Day of Colonoscopy or Day 30.

There were also 408 patients who participated in a study in which either SUPREP Bowel Prep Kit or PEG+E were administered in an evening-only (1-day) regimen. Higher rates of overall discomfort, abdominal distention, and nausea were observed with the evening-only (1-day) regimen compared to the split-dose (2-day) regimen for both preparations. Patients treated with SUPREP Bowel Prep Kit had increased rates of vomiting with the evening-only (1-day) regimen. An evening-only (1-day) dosing regimen was associated with higher rates of abnormal values for some electrolytes when compared to the split-dose (2-day) regimen for both preparations. For SUPREP Bowel Prep Kit, the evening only (1-day) regimen was associated with higher rates of total bilirubin (high), BUN (high), creatinine (high), osmolality (high), potassium (high) and uric acid (high) than the SUPREP Bowel Prep Kit split dose (2-day) regimen. Administration of SUPREP Bowel Prep Kit in an evening-only (1-day) dosing regimen is *not* recommended.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Risks Due to Fluid and Electrolyte Abnormalities

Use caution when prescribing SUPREP Bowel Prep Kit for patients with conditions, or who are using medications, that increase the risk for fluid and electrolyte disturbances or may increase the risk of adverse events of seizure, arrhythmias, and prolonged QT in the setting of fluid and electrolyte abnormalities. Consider additional patient evaluations as appropriate [*see Warnings (5)*] in patients taking these concomitant medications.

7.2 Potential for Altered Drug Absorption

Oral medication administered within one hour of the start of each SUPREP Bowel Prep Kit dose may be flushed from the gastrointestinal tract, and the medication may not be absorbed properly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with SUPREP Bowel Prep Kit. It is also not known whether SUPREP Bowel Prep Kit can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SUPREP Bowel Prep Kit should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUPREP Bowel Prep Kit is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

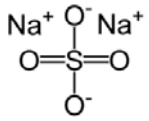
8.5 Geriatric Use

Of the 375 patients who received SUPREP Bowel Prep Kit in clinical trials, 94 (25%) were 65 years of age or older, and 25 (7%) were 75 years of age or older. No overall differences in safety or effectiveness of SUPREP Bowel Prep Kit administered as a split-dose (2-day) regimen were observed between geriatric patients and younger patients. Geriatric patients reported more vomiting when SUPREP Bowel Prep Kit was given as a one-day preparation.

11 DESCRIPTION

Each SUPREP Bowel Prep Kit contains two 6 ounce bottles of solution. Each 6 ounce bottle contains: sodium sulfate 17.5 grams, potassium sulfate 3.13 grams, magnesium sulfate 1.6 grams. Inactive ingredients include: sodium benzoate, NF, sucralose, malic acid FCC, citric acid USP, flavoring ingredients, purified water, USP. The solution is a clear to slightly hazy liquid. The solution is clear and colorless when diluted to a final volume of 16 ounces with water.

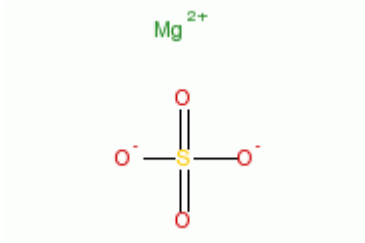
Sodium Sulfate, USP
The chemical name is Na_2SO_4. The average Molecular Weight is 142.04. The structural formula is:



Potassium Sulfate, FCC, purified

The chemical name is K_2SO_4. The average Molecular Weight is 174.26. The structural formula is:

Magnesium Sulfate, USP
The chemical name is $MgSO_4$. The average Molecular Weight: 120.37. The structural formula is:



Each SUPREP Bowel Prep Kit also contains a polypropylene mixing container.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sulfate salts provide sulfate anions, which are poorly absorbed. The osmotic effect of unabsorbed sulfate anions and the associated cations causes water to be retained within the gastrointestinal tract.

12.2 Pharmacodynamics

The osmotic effect of the unabsorbed ions, when ingested with a large volume of water, produces a copious watery diarrhea.

12.3 Pharmacokinetics

Fecal excretion was the primary route of sulfate elimination. After administration of SUPREP Bowel Prep Kit in six healthy volunteers, the time at which serum sulfate reached its highest point (T_{max}) was approximately 17 hours after the first half dose or approximately 5 hours after the second dose, and then declined with a half-life of 8.5 hours.

The disposition of sulfate after SUPREP Bowel Prep Kit was also studied in patients (N=6) with mild-moderate hepatic impairment (Child-Pugh grades A and B) and in patients (N=6) with moderate renal impairment (creatinine clearance of 30 to 49 mL/min). The renal impairment group had the highest serum sulfate AUC and C_{max}, followed by the hepatic impairment group, and then by healthy subjects. Systemic exposure of serum sulfate (AUC and

C_{max}) was similar between healthy subjects and hepatic impairment patients. Renal impairment resulted in 54% higher mean AUC and 44% higher mean C_{max} than healthy subjects. The mean sulfate levels of all three groups returned to their respective baseline levels by Day 6 after dose initiation. Urinary excretion of sulfate over 30 hours, starting after the first half dose, was similar between hepatic patients and normal volunteers, but was approximately 16% lower in moderate renal impairment patients than in healthy volunteers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of SUPREP Bowel Prep Kit. Studies to evaluate the possible impairment of fertility or mutagenic potential of SUPREP Bowel Prep Kit have not been performed.

13.2 Animal Toxicology and/or Pharmacology

The sulfate salts of sodium, potassium, and magnesium contained in SUPREP Bowel Prep Kit were administered orally (gavage) to rats and dogs up to 28 days up to a maximum daily dose of 5 grams/kg/day (approximately 0.9 and 3 times for rats and dogs, respectively, the recommended human dose of 44 grams/day or 0.89 grams/kg based on the body surface area). In rats, the sulfate salts caused diarrhea and electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia, lower serum osmolality, and high serum bicarbonate. Significant renal changes included increased fractional sodium excretion, increased urinary sodium and potassium excretion, and alkaline urine in both males and females. In addition, creatinine clearance was significantly decreased in females at the highest dose. No microscopic renal changes were seen. In dogs, the sulfate salts caused emesis, excessive salivation, excessive drinking of water, and abnormal excreta (soft and/or mucoid feces and/or diarrhea) and increased urine pH and sodium excretion.

14 CLINICAL STUDIES

The colon cleansing efficacy of SUPREP Bowel Prep Kit was evaluated in a randomized, single-blind, active-controlled, multicenter study. In this study, 363 adult patients were included in the efficacy analysis. Patients ranged in age from 20 to 84 years (mean age 55 years) and 54% were female. Race distribution was 86% Caucasian, 9% African-American, and 5% other.

Patients were randomized to one of the following two colon preparation regimens: SUPREP Bowel Prep Kit or a marketed polyethylene glycol (PEG) bowel prep. In the Study SUPREP Bowel Prep Kit was administered according to a split-dose preparation regimen [*see Dosage and Administration (2.1)*]. The PEG bowel prep was also given as a split-dose preparation according to its labeled instructions. Patients receiving SUPREP Bowel Prep Kit were limited to a light breakfast followed by clear liquids on the day prior to the day of colonoscopy; patients receiving the PEG bowel prep were allowed to have a normal breakfast and a light lunch, followed by clear liquids.

The primary efficacy endpoint was the proportion of patients with successful colon cleansing as assessed by the colonoscopists, who were not informed about the type of preparation received. In the study, no clinically or statistically significant differences were seen between the group treated with SUPREP Bowel Prep Kit and the group treated with the PEG bowel prep. See Table 3 below.

Table 3: Colon Cleansing Response Rates

Treatment Group	Regimen	N	Responders[1] % (95% C. I.)	SUPREP – PEG Difference (95% CI)
SUPREP Bowel Prep Kit (with light breakfast)	Split-Dose	180	**97%** (94%, 99%)	**2%**[2] (-2%, 5%)
PEG bowel prep (with normal breakfast & light lunch)	Split-Dose	183	**96%** (92%, 98%)	

[1] Responders were patients whose colon preparations were graded excellent (no more than small bits of adherent feces/fluid) or good (small amounts of feces or fluid not interfering with the exam) by the colonoscopist.
[2] Does not equal difference in tabled responder rates due to rounding effects.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each SUPREP Bowel Prep Kit contains:

- Two (2) 6 ounce bottles of oral solution.
- One (1) 19 ounce mixing container with a 16 ounce fill line.

Storage:
Store at 20º to 25°C (68º to 77°F). Excursions permitted between 15º to 30°C (59º to 86°F). See USP controlled room temperature.

Keep out of reach of children.

SUPREP Bowel Prep Kit NDC 52268-012-01

17 PATIENT COUNSELING INFORMATION

See Medication Guide and FDA-Approved Patient Labeling

17.1 Patient Counseling

- Ask patients to let you know if they have trouble swallowing or are prone to regurgitation or aspiration.

- Instruct patients that each bottle needs to be diluted in water before ingestion and that they need to drink additional water according to the instructions. Direct ingestion of the undiluted solution may increase the risk of nausea, vomiting, and dehydration.
- Inform patients that oral medications may not be absorbed properly if they are taken within one hour of starting each dose of SUPREP Bowel Prep Kit.
- Tell patients not to take other laxatives while they are taking SUPREP Bowel Prep Kit.

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