HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Prepopik® safely and effectively. See full prescribing information for Prepopik®.

Prepopik® (sodium picosulfate, magnesium oxide, and anhydrous citric acid) for oral solution
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------
Prepopik® is a combination of sodium picosulfate, a stimulant laxative, and magnesium oxide and anhydrous citric acid which form magnesium citrate, an osmotic laxative, indicated for cleansing of the colon as a preparation for colonoscopy in adults (1)

----------DOSAGE AND ADMINISTRATION----------
- Prepopik®, supplied as a powder, must be reconstituted with cold water right before its use (2.1, 2.2)
- Two dosing regimens, each requires two separate dosing times (2.1)
- "Split-Dose" method is preferred method (2.3)
  - First dose: during evening before the colonoscopy
  - Second dose: next day, during the morning prior to the colonoscopy
- "Day-Before" method is alternative method if "Split-Dose" is not appropriate (2.4)
  - First dose: during afternoon or early evening before the colonoscopy
  - Second dose: 6 hours later during evening before colonoscopy
- Additional clear liquids (no solid food or milk) must be consumed after every dose in both dosing regimens (2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For oral solution: Each of 2 packets contains 16.1 g of powder for orange flavor or 16.2 grams of powder for cranberry flavor : 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid (3)

----------CONTRAINDICATIONS----------
- Patients with severely reduced renal function (creatinine clearance less than 30 mL/minute) (4)
- Gastrointestinal (GI) obstruction or ileus (4)
- Bowel perforation (4)
- Toxic colitis or toxic megacolon (4)
- Gastric retention (4)

----------WARNINGS AND PRECAUTIONS----------
- *Risk of fluid and electrolyte abnormalities, arrhythmia, seizures, and renal impairment:* Encourage adequate hydration, assess concurrent medications, and consider laboratory assessments prior to and after use (5.1, 5.2, 5.3, 5.4)
- *Risks in patients with renal insufficiency or patients taking concomitant medications that affect renal function:* Use caution, ensure adequate hydration and consider testing (5.3)
- *Mucosal ulcerations:* Consider potential for mucosal ulcerations when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease (5.5)
- *Suspected GI obstruction or perforation:* Rule out diagnosis before administration (4, 5.6)
- *Patients at risk for aspiration:* Observe during administration (5.7)
- *Not for direct ingestion:* Dissolve and take with additional water (5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>1%) are nausea, headache and vomiting (abdominal bloating, distension, pain/cramping, and watery diarrhea not requiring an intervention were not collected) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ferring at 1-888-FERRING (1-888-337-7464) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Drugs that increase risks due to fluid and electrolyte change (7.1)
- *Oral medication taken within 1 hour of start of each dosing:* Might not be properly absorbed (7.2)
- *Antibiotics:* Prior or concomitant use of antibiotics may reduce efficacy of Prepopik®(7.3)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Prepopik® should be used during pregnancy only if clearly needed (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Prepopik® (sodium picosulfate, magnesium oxide and anhydrous citric acid) for oral solution is indicated for cleansing of the colon as a preparation for colonoscopy in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Overview

Prepopik®, supplied as a powder, must be reconstituted with cold water right before its use *[see Dosage and Administration (2.2)]*. There are two dosing regimens, each requires two separate dosing times:

- The preferred method is the "Split-Dose" method and consists of two separate doses: the first dose during the evening before the colonoscopy and the second dose the next day, during the morning prior to the colonoscopy *[see Dosage and Administration (2.3)]*
- The alternative method is the "Day Before" method and consists of two separate doses: the first dose during the afternoon or early evening before the colonoscopy and the second dose 6 hours later during the evening before the colonoscopy *[see Dosage and Administration (2.4)]*.

Additional fluids must be consumed after every dose in both dosing regimens *[see Dosage and Administration (2.3, 2.4)]*. Instruct patients to consume only clear liquids (no solid food or milk) on the day before the colonoscopy up until 2 hours before the time of the colonoscopy. Instruct patients that if they experience severe bloating, distention, or abdominal pain following the first dose, delay the second dose until their symptoms resolve.

2.2 Reconstitution of the Prepopik® Powder

(a) Reconstitute the Prepopik® powder right before each administration. Do not prepare the solution in advance.
(b) Fill the supplied dosing cup with cold water up to the lower (5-ounce) line on the cup and pour in the contents of one packet of Prepopik® powder.
(c) Stir for 2 to 3 minutes. The reconstituted Prepopik® solution may become slightly warm as the powder dissolves.

2.3 Split-Dose Dosing Regimen (Preferred Method)

The Split-Dose regimen is the preferred dosing method. Instruct patients to take two separate doses in conjunction with fluids, as follows:

- Take the first dose during the evening before the colonoscopy (e.g., 5:00 to 9:00 PM) followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before bed. Consume clear liquids within 5 hours.
- Take second dose the next day approximately 5 hours before the colonoscopy followed by at least three 8-ounce drinks of clear liquids before the colonoscopy. Consume clear liquids within 5 hours up until 2 hours before the time of the colonoscopy.

2.4 Day-Before Dosing Regimen (Alternative Method)

The Day-Before regimen is the alternative dosing method for patients for whom the Split-Dosing is inappropriate. Instruct patients to take two separate doses in conjunction with fluids, as follows:

- Take the first dose in the afternoon or early evening (e.g., 4:00 to 6:00 PM) before the colonoscopy followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before the next dose. Consume clear liquids within 5 hours.
- Take the second dose approximately 6 hours later in the late evening (e.g., 10:00 PM to 12:00 AM), the night before the colonoscopy followed by three 8-ounce drinks of clear liquids before bed. Consume clear liquids within 5 hours.

3 DOSAGE FORMS AND STRENGTHS

For oral solution: Each of the two packets contains 10 mg of sodium picosulfate, 3.5 grams of magnesium oxide, and 12.0 grams of anhydrous citric acid in 16.1grams of powder for orange flavor or 16.2 grams of powder for cranberry flavor.

4 CONTRAINDICATIONS

Prepopik® is contraindicated in the following conditions:

- Patients with severely reduced renal function (creatinine clearance less than 30 mL/minute) which may result in accumulation of magnesium *[see Warnings and Precautions (5.3)]*
- Gastrointestinal obstruction or ileus *[see Warnings and Precautions (5.6)]*
- Bowel perforation
- Toxic colitis or toxic megacolon
- Gastric retention
- An allergy to any of the ingredients in Prepopik®

5 WARNINGS AND PRECAUTIONS

5.1 Serious Fluid and Serum Chemistry Abnormalities

Advise patients to hydrate adequately before, during, and after the use of Prepopik®. Use caution in patients with congestive heart failure when replacing fluids. If a patient develops significant vomiting or signs of dehydration including signs of orthostatic hypotension after taking Prepopik®, consider performing post-colonoscopy lab tests (electrolytes, creatinine, and BUN) and treat accordingly. Approximately 20% of patients in both arms (Prepopik®, 2L of PEG + E plus two x 5-mg bisacodyl tablets) of clinical trials of Prepopik® had orthostatic changes (changes in blood pressure and/or heart rate) on the day of colonoscopy. In clinical trials orthostatic changes were documented out to seven days post colonoscopy. *[see Adverse Reactions (6.1, 6.2)]*

Fluid and electrolyte disturbances can lead to serious adverse events including cardiac arrhythmias or seizures and renal impairment. Fluid and electrolyte abnormalities should be corrected before treatment with Prepopik®. In addition, use caution when prescribing Prepopik® for patients who have conditions or who are using medications that increase the risk for fluid and electrolyte disturbances or that may increase the risk of adverse events of seizure, arrhythmia, and renal impairment.

5.2 Seizures

There have been reports of generalized tonic-clonic seizures with the 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 Prepopik® for patients with a history of seizures and in patients at risk of seizure, such as patients taking medications that lower the seizure threshold (e.g., tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, patients with known or suspected hyponatremia. *[see Adverse Reactions (6.2)]*

5.3 Use in Patients with Renal Impairment

As in other magnesium containing bowel preparations, use caution when prescribing Prepopik® 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). These patients may be at increased risk for renal injury. Advise these patients of the importance of adequate hydration before, during and after the use of Prepopik®. Consider performing baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in these patients. In patients with severely reduced renal function (creatinine clearance < 30 mL/min), accumulation of magnesium in plasma may occur.

5.4 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 Prepopik® 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.

5.5 Colonic Mucosal Ulceration, Ischemic Colitis and Ulcerative Colitis

Osmotic laxatives may produce colonic mucosal aphthous ulcerations and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Concurrent use of additional stimulant laxatives with Prepopik® may increase this risk. The potential for mucosal ulcerations should be considered when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease. *[see Adverse Reactions (6.2)]*

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 Prepopik®. Use with caution in patients with severe active ulcerative colitis.

5.7 Aspiration

Patients with impaired gag reflex and patients prone to regurgitation or aspiration should be observed during the administration of Prepopik®. Use with caution in these patients.

5.8 Not for Direct Ingestion

Each packet must be dissolved in 5 ounces of cold water and administered at separate times according to the dosing regimen. Ingestion of additional water is important to patient tolerance. Direct ingestion of the undissolved powder may increase the risk of nausea, vomiting, dehydration, and electrolyte disturbances.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

In randomized, multicenter, controlled clinical trials, nausea, headache, and vomiting were the most common adverse reactions (>1%) following Prepopik® administration. The patients were not blinded to the study drug. Since abdominal bloating, distension, pain/cramping, and watery diarrhea are known to occur in response to colon cleansing preparations, these effects were documented as adverse events in the clinical trials only if they required medical intervention (such as a change in study drug or led to study discontinuation, therapeutic or diagnostic procedures, met the criteria for a serious adverse event), or showed clinically significant worsening during the study that was not in the frame of the usual clinical course, as determined by the investigator.

Prepopik® was compared for colon cleansing effectiveness with a preparation containing two liters (2L) of polyethylene glycol plus electrolytes solution (PEG + E) and two 5-mg bisacodyl tablets, all administered the day before the procedure. Table 1 displays the most common adverse reactions in Study 1 and Study 2 for the Prepopik® Split-Dose and Day-Before dosing regimens, respectively, each as compared to the comparator preparation.

Table 1: Treatment-Emergent Adverse Reactions observed in at Least (>1%) of Patients using the Split-Dose Regimen and Day-Before Regimen **

	Study 1: Split-Dose Regimen		**Study 2: Day-Before Regimen**	
Adverse Reaction	**PREPOPIK® (N=305) n (% = n/N)**	**2L PEG+E* with 2 x 5-mg bisacodyl tablets (N=298) n (% = n/N)**	**PREPOPIK® (N=296) n (% = n/N)**	**2L PEG+E* with 2 x 5-mg bisacodyl tablets (N=302) n (% = n/N)**
Nausea	8 (2.6)	11 (3.7)	9 (3.0)	13 (4.3)
Headache	5 (1.6)	5 (1.7)	8 (2.7)	5 (1.7)
Vomiting	3 (1.0)	10 (3.4)	4 (1.4)	6 (2.0)

* 2L PEG + E = two liters polyethylene glycol plus electrolytes solution.

**abdominal bloating, distension, pain/cramping, and watery diarrhea not requiring an intervention were not collected

Electrolyte Abnormalities

In general, Prepopik® was associated with numerically higher rates of abnormal electrolyte shifts on the day of colonoscopy compared to the preparation containing 2L of PEG + E plus two x 5-mg bisacodyl tablets (Table 2). These shifts were transient in nature and numerically similar between treatment arms at the Day 30 visit.

Table 2: Shifts from Normal Baseline to Outside the Normal Range at Day 7 and Day 30

Laboratory Parameter (direction of change)	Visit	Study 1: Split-Dose Regimen		Study 2: Day-Before Regimen	
		PREPOPIK®	2L PEG+E with 2x 5 mg bisacodyl tablets	PREPOPIK®	2L PEG+E with 2x 5 mg bisacodyl tablets
		n/N (%)		n/N (%)	
Potassium (low)	Day of Colonoscopy	19/260 (7.3)	11/268 (4.1)	13/274 (4.7)	13/271 (4.8)
	24-48 hours	3/302 (1.0)	2/294 (0.7)	3/287 (1.0)	5/292 (1.7)
	Day 7	11/285 (3.9)	8/279 (2.9)	6/276 (2.2)	14/278 (5.0)
	Day 30	11/284 (3.9)	8/278 (2.9)	7/275 (2.5)	8/284 (2.8)
Sodium (low)	Day of Colonoscopy	11/298 (3.7)	3/295 (1.0)	3/286 (1.0)	3/295 (1.0)
	24-48 hours	1/303 (0.3)	1/295 (0.3)	1/288 (0.3)	1/293 (0.3)
	Day 7	2/300 (0.7)	1/292 (0.3)	1/285 (0.4)	1/291 (0.3)

	Day 30	2/299(0.7)	3/291 (1.0)	1/284(0.4)	1/296 (0.3)
Chloride (low)	Day of Colonoscopy	11/301 (3.7)	1/298 (0.3)	3/287 (1.0)	0/297 (0.0)
	24-48 hours	1/303 (0.3)	0/295 (0.0)	2/288 (0.7)	0/293 (0.0)
	Day 7	1/303 (0.3)	3/295 (1.0)	0/285 (0.0)	0/293 (0.0)
	Day 30	2/302 (0.7)	3/294 (1.0)	0/285 (0.0)	0/298 (0.0)
Magnesium (high)	Day of Colonoscopy	34/294 (11.6)	0/294 (0.0)	25/288 (8.7)	1/289 (0.3)
	24-48 hours	0/303 (0.0)	0/295 (0.0)	0/288 (0.0)	0/293 (0.0)
	Day 7	0/297 (0.0)	1/291 (0.3)	1/286 (0.3)	1/285 (0.4)
	Day 30	1/296 (0.3)	2/290 (0.7)	0/286 (0.0)	0/290 (0.0)
Calcium (low)	Day of Colonoscopy	2/292 (0.7)	1/286 (0.3)	0/276 (0.0)	2/282 (0.7)
	24-48 hours	0/303 (0.0)	0/295 (0.0)	0/288 (0.0)	0/293 (0.0)
	Day 7	0/293 (0.0)	1/283 (0.4)	0/274 (0.0)	0/278 (0.0)
	Day 30	0/292 (0.0)	1/282 (0.4)	0/274 (0.0)	1/283 (0.4)
Creatinine (high)	Day of Colonoscopy	5/260 (1.9)	13/268 (4.9)	12/266 (4.5)	16/270 (5.9)
	24-48 hours	1/303 (0.3)	0/295 (0.0)	0/288 (0.0)	0/293 (0.0)
	Day 7	10/264 (0.4)	13/267 (4.8)	10/264 (3.8)	10/265 (3.8)
	Day 30	11/264 (4.2)	14/265(5.3)	18/264 (6.8)	10/272 (3.7)
eGFR (low)	Day of Colonoscopy	22/221 (10.0)	17/214 (7.9)	26/199 (13.1)	25/224 (11.2)
	24-48 hours	76/303 (25.1)	72/295 (24.4)	82/288 (28.5)	62/293 (21.2)
	Day 7	22/223 (10.0)	17/213 (8.0)	11/198 (5.6)	28/219 (12.8)
	Day 30	24/223(10.8)	21/211 (10.0)	21/199 (10.6)	24/224 (10.7)

6.2 Postmarketing Experience

The following foreign spontaneous reports have been identified during use of formulations similar to Prepopik®. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic reactions

Cases of hypersensitivity reactions including rash, urticaria, and purpura have been reported.

Electrolyte abnormalities

There have been reports of hypokalemia, hyponatremia and hypermagnesemia with the use of Prepopik® for colon preparation prior to colonoscopy.

Gastrointestinal:

Abdominal pain, diarrhea, fecal incontinence, and proctalgia have been reported with the use of Prepopik® for colon preparation prior to colonoscopy. There have been isolated reports of reversible aphthoid ileal ulcers. Ischemic colitis has been reported with the use of Prepopik® for colon preparation prior to colonoscopy. However, a causal relationship between these ischemic colitis cases and the use of Prepopik® has not been established.

Neurologic,

There have been reports of generalized tonic-clonic seizures associated with and without hyponatremia in epileptic patients.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Risks of Fluid and Electrolyte Abnormalities

Use caution when prescribing Prepopik® for patients with conditions or who are using medications that increase the risk for fluid and electrolyte disturbances or may increase the risk of seizure, arrhythmias, and prolonged QT in the setting of fluid and electrolyte abnormalities. This includes patients receiving drugs which may be associated with hypokalemia (such as diuretics or corticosteroids, or drugs where hypokalemia is a particular risk, such as cardiac glycosides) or hyponatremia. Use caution when Prepopik® is used in patients on nonsteroidal anti-inflammatory drugs (NSAIDS) or drugs known to induce Antidiuretic Hormone Secretion (SIADH), such as tricyclic antidepressants, selective serotonin re-uptake inhibitors, antipsychotic drugs and carbamazepine, as these drugs may increase the risk of water retention and/or electrolyte imbalance. Consider additional patient evaluations as appropriate. *[see Adverse Reactions (6.1, 6.2)]*

7.2 Potential for Altered Drug Absorption

Oral medication administered within one hour of the start of administration of Prepopik® solution may be flushed from the GI tract and the medication may not be absorbed.

Tetracycline and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine and penicillamine, should be taken at least 2 hours before and not less than 6 hours after administration of Prepopik® to avoid chelation with magnesium.

7.3 Antibiotics
Prior or concomitant use of antibiotics with Prepopik® may reduce efficacy of Prepopik® as conversion of sodium picosulfate to its active metabolite BHPM is mediated by colonic bacteria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies with Prepopik® have been performed in pregnant rats at oral doses up to 2000 mg/kg/day (about 1.2 times the recommended human dose based on the body surface area), and did not reveal any evidence of impaired fertility or harm to the fetus due to Prepopik®. The reproduction study in rabbits was not adequate, as treatment-related mortalities were observed at all doses. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on the body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Prepopik® should be used during pregnancy 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 Prepopik® is administered to a nursing woman.

8.4 Pediatric Use
The safety and effectiveness of Prepopik® in pediatric patients has not been established.

8.5 Geriatric Use
In controlled clinical trials of Prepopik®, 215 of 1201 (18%) patients were 65 years of age or older. The overall incidence of treatment-emergent adverse events was similar among patients ≥65 years of age (73%) and patients <65 years of age (71%). Among all patients ≥65 years of age, the proportion of patients with successful colon cleansing was greater in the Prepopik® group (81.1%) than in the comparator group (70.9%).

8.6 Renal Insufficiency
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) may be at increased risk for further renal injury. Advise these patients of the importance of adequate hydration before, during and after the use of Prepopik®. Consider performing baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in these patients. In patients with severely reduced renal function (creatinine clearance < 30 mL/min), accumulation of magnesium in plasma may occur. The signs and symptoms of hypermagnesemia may include, but are not limited to, diminished or absent deep tendon reflexes, somnolence, hypocalcemia, hypotension, bradycardia, muscle, respiratory paralysis, complete heart block, and cardiac arrest.

10 OVERDOSAGE
The patient who has taken an overdose should be monitored carefully, and treated symptomatically for complications.

11 DESCRIPTION
Prepopik® (sodium picosulfate, magnesium oxide and anhydrous citric acid) for oral solution is available in 2 flavors, orange and cranberry flavor, and is provided in two packets. The contents of each is to be dissolved in 5 ounces of cold water and consumed.

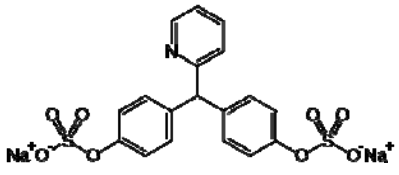
Each packet for both flavors contains 10 mg sodium picosulfate, 3.5 g magnesium oxide and 12 g anhydrous citric acid. The product also contains the following inactive ingredients: potassium hydrogen carbonate, saccharine sodium and orange or cranberry flavors. The orange flavor contains acacia gum, lactose, ascorbic acid and butylated hydroxyanisole, and the cranberry flavor contains

maltodextrin, glyceryl triacetate (triacetin) and sodium octenyl succinated starch. The following is a description of the three active ingredients:

Sodium picosulfate is a stimulant laxative.

Sodium picosulfate

- Chemical name: 4,4′-(2-pyridylmethylene) diphenyl bis(hydrogen sulfate) disodium salt, monohydrate
- Chemical formula: $C_{18}H_{13}NNa_2O_8S_2.H_2O$
- Molecular weight: 499.4
- Structural formula:



- Sodium picosulfate

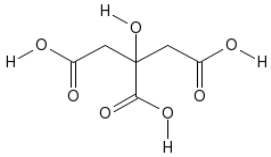
Magnesium citrate, which is formed in solution by the combination of magnesium oxide and anhydrous citric acid, is an osmotic laxative.

Magnesium oxide

- Chemical name: Magnesium oxide
- Chemical formula: Mg O
- Molecular weight: 40.3
- Structural formula: Mg O

Anhydrous citric acid

- Chemical name: 2-hydroxypropane-1,2,3-tricarboxylic acid
- Chemical formula: $C_6H_8O_7$
- Molecular weight: 192.1
- Structural formula:



Anhydrous citric acid

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium picosulfate is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM, which acts directly on the colonic mucosa to stimulate colonic peristalsis.
Magnesium oxide and citric acid react to create magnesium citrate in solution, which is an osmotic agent that causes water to be retained within the gastrointestinal tract.

12.2 Pharmacodynamics

The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a purgative effect which, when ingested with additional fluids, produces watery diarrhea.

12.3 Pharmacokinetics

Sodium picosulfate, which is a prodrug, is converted to its active metabolite, BHPM, by colonic bacteria. After administration of 2 packets of Prepopik® separated by 6 hours, in 16 healthy volunteers, sodium picosulfate reached a mean C_{max} of 3.2 ng/mL at approximately 7 hours (T_{max}). After the first packet the corresponding values were 2.3 ng/mL at 2 hours. The terminal half-life of sodium picosulfate was 7.4 hours. The fraction of the absorbed sodium picosulfate dose excreted unchanged in urine was 0.19%. Plasma levels of the free BHPM were low, with 13 out of 16 subjects studied having plasma BHPM concentrations below the lower limit of quantification (0.1 ng/mL). Urinary samples show that the majority of excreted BHPM was in the glucuronide-conjugated form. Magnesium oxide and citric acid react in water to create magnesium citrate. Baseline uncorrected magnesium concentration reached a maximum (C_{max}) of approximately 1.9 mEq/L, which occurred at 10 hours post initial packet administration (T_{max}). This represents an approximately 20% increase from the baseline.

Drug Interaction Studies

In an *in vitro* study using human liver microsomes, sodium picosulfate did not inhibit the major CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) evaluated. Based on an *in vitro* study using freshly isolated hepatocyte culture, sodium picosulfate is not an inducer of CYP1A2, CYP2B6 or CYP3A4/5.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with Prepopik®. However, sodium picosulfate was not mutagenic in the Ames test, the mouse lymphoma assay and the mouse bone marrow micronucleus test.

In an oral fertility study in rats, Prepopik® did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 2000 mg/kg twice daily (about 1.2 times the recommended human dose based on the body surface area).

14 CLINICAL STUDIES

The colon cleansing efficacy of Prepopik® was evaluated for non-inferiority against a comparator in two randomized, investigator-blinded, active-controlled, multicenter US trials in patients scheduled to have an elective colonoscopy. In all, 1195 adult patients were included in the primary efficacy analysis: 601 from Study 1, and 594 from Study 2. Patients ranged in age from 18 to 80 years (mean age 56 years); 61% were female and 39% male. Self-identified race was distributed as follows: 90% White, 10% Black, and less than 1% other. Of these, 3% self-identified their ethnicity as Hispanic or Latino.

Patients randomized to Prepopik® in the two studies were treated with one of two dosing regimens:

- In Study 1, Prepopik® was given by "Split-Dose" (evening before and day of) dosing, where the first packet was taken the evening before the colonoscopy (between 5:00 and 9:00 PM), followed by five (5) 8-ounce glasses of clear liquid, and the second packet was taken the morning of the colonoscopy (at least 5 hours prior to but no more than 9 hours prior to colonoscopy), followed by three (3) 8-ounce glasses of clear liquid.
- In Study 2, Prepopik® was given by "Day-Before" (afternoon/evening before only) dosing, where both packets were taken separately on the day before the colonoscopy, with the first packet taken in the afternoon (between 4:00 and 6:00 PM), followed by five (5) 8-ounce glasses of clear liquid, and the second packet taken in the late evening (approximately 6 hours later, between 10:00 PM and 12:00 AM), followed by three (3) 8-ounce glasses of clear liquid.

The comparator was a preparation containing two liters of polyethylene glycol plus electrolytes solution (PEG + E) and two 5-mg bisacodyl tablets, administered the day before the procedure. All patients in both the Prepopik® and comparator groups were limited to a clear liquid diet on the day before the procedure (24 hours before).

The primary efficacy endpoint was the proportion of patients with successful colon cleansing, as assessed by blinded colonoscopists using the Aronchick Scale. The Aronchick scale is a tool used to assess overall colon cleansing. Successful colon cleansing was defined as bowel preparations with >90% of the mucosa seen and mostly liquid stool that were graded excellent (minimal suctioning needed for adequate visualization) or good (significant suctioning needed for adequate visualization) by the colonoscopist.

In both studies, Prepopik® was non-inferior to the comparator. In addition, Prepopik® provided by Split-Dose dosing met the pre-specified criteria for superiority to the comparator for colon cleansing in Study 1. The comparator in that study was administered entirely on the day prior to colonoscopy. See Tables 3 and 4 below.

Table 3: Proportion of Patients with Successful Colon Cleansing in Study 1 Split-Dose Regimen

PREPOPIK® Split-Dose Regimen	2L PEG+E* with 2 x 5-mg bisacodyl tablets	Difference between treatment groups

% (n/N)	% (n/N)	Difference	95% CI
84.2% (256/304)	74.4% (221/297)	9.8%	(3.4%, 16.2%)†

* 2L PEG + E = two liters polyethylene glycol plus electrolytes solution.

† Non-inferior and superior 2L PEG+E with 2 x 5-mg bisacodyl tablets

Table 4: Proportion of Patients with Successful Colon Cleansing in Study 2 Day-Before Regimen

PREPOPIK® Day-Before Regimen	2L PEG+E* with 2 x 5-mg bisacodyl tablets	Difference between treatment groups	
% (n/N)	% (n/N)	Difference	95% CI
83.0% (244/294)	79.7% (239/300)	3.3%	(-2.9%, 9.6%)‡

* 2L PEG + E = two liters polyethylene glycol plus electrolytes solution.

‡ Non-inferior

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Prepopik® is supplied in a carton containing 2 packets, each holding 16.1 grams of powder in orange flavor or 16.2 grams of powder in cranberry flavor for oral solution, along with a pre-marked dosing cup. Each packet for both flavors contains 10 mg sodium picosulfate, 3.5 g magnesium oxide and 12 g anhydrous citric acid. The excipients for both flavors include potassium hydrogen carbonate, sodium saccharin, orange or cranberry flavor. The orange flavor contains acacia gum, lactose, ascorbic acid, and butylated hydroxyanisole, and the cranberry flavor contains maltodextrin, glyceryl triacetate (triacetin) and sodium octenyl succinated starch.

Storage

Store at 25°C (77°F). Excursions permitted at 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Orange flavor:
NDC# 55566-9300-2 Kit, 2 packets and cup

Cranberry flavor:
NDC# 55566-9700-1- Kit, 2 packets and cup

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

- Ask patients to let you know if they have trouble swallowing or are prone to regurgitation or aspiration.
- Tell patients not to take other laxatives while they are taking Prepopik®.
- Tell patients that if they experience severe bloating, distention or abdominal pain following the first packet of Prepopik®, delay the second administration until the symptoms resolve.
- Instruct patients to contact their healthcare provider if they develop signs and symptoms of dehydration.
- Not for Direct Ingestion: Each packet must be dissolved in 5 ounces of cold water and administered at separate times according to the dosing regimen. Ingestion of additional water is important to patient tolerance. Direct ingestion of the undissolved powder may increase the risk of nausea, vomiting, dehydration, and electrolyte disturbances. Inform patients that oral medication administered within one hour of the start of administration of Prepopik® solution may not be absorbed completely.

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No. 6 HuiLing Lu (Ferring Road)
National Health Technology Park
Zhongshan City, Guangdong Province, CHINA

Manufactured for:
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Parsippany, N.J. 07054

8109000012
Rev. 04/2015

Medication Guide

PREPOPIK® (prep-ō-pik)
(sodium picosulfate, magnesium oxide and anhydrous citric acid) for oral solution

Read this Medication Guide instructions before you start taking PREPOPIK® and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PREPOPIK®?

PREPOPIK® and other bowel preparations can cause serious side effects, including:

Serious loss of body fluid (dehydration) and changes in blood salts (electrolytes) in your blood. These changes can cause:

- abnormal heartbeats that can cause death
- seizures. This can happen even if you have never had a seizure.
- kidney problems

Your chance of having fluid loss and changes in blood salts with PREPOPIK® is higher if you:

- have heart problems
- have kidney problems
- take water pills or non-steroidal anti-inflammatory drugs (NSAIDS)

Tell your healthcare provider right away if you have any of these symptoms of a loss of too much body fluid (dehydration) while taking PREPOPIK®:

- vomiting that prevents you from keeping down the additional prescribed amounts of clear liquids that you must drink after taking your PREPOPIK®
- dizziness
- urinating less often than normal
- headache

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

What is PREPOPIK®?

PREPOPIK® is a prescription medicine used by adults to clean the colon before a colonoscopy. PREPOPIK® cleans your colon by causing you to have diarrhea. Cleaning your colon helps your healthcare provider see the inside of your colon more clearly during your colonoscopy.

It is not known if PREPOPIK® is safe and effective in children.

Who should not take PREPOPIK®?

Do not take PREPOPIK® if your healthcare provider has told you that you have:

- serious kidney problems
- a blockage in your intestine (bowel obstruction)
- an opening in the wall of your stomach or intestines (bowel perforation)
- a very dilated intestine (toxic megacolon)
- problems with the emptying of food and fluid from your stomach (gastric retention)
- an allergy to any of the ingredients in PREPOPIK®. See the end of this leaflet for a complete list of ingredients in PREPOPIK®.

What should I tell my healthcare provider before taking PREPOPIK®?

Before you take PREPOPIK®, tell your healthcare provider if you:

- have heart problems
- have stomach or bowel problems
- have ulcerative colitis
- have problems with swallowing or gastric reflux
- are withdrawing from drinking alcohol and benzodiazepines
- have kidney problems
- have low blood salt (sodium) level
- any other medical conditions
- are pregnant. It is not known if PREPOPIK® will harm your unborn baby. Talk to your provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if PREPOPIK® passes into your breast milk. You and your healthcare provider should decide if you will take PREPOPIK® while breastfeeding.

Tell your healthcare provider about all the medicines you take,
including prescription and non-prescription medicines, vitamins, and herbal supplements.

PREPOPIK® may affect how other medicines work. Medicines taken by mouth may not be absorbed properly when taken within 1 hour before the start of PREPOPIK®.

Especially tell your healthcare provider if you take:

- medicines for blood pressure or heart problems
- medicines for kidney problems
- medicines for seizures
- water pills (diuretics)
- nonsteroidal anti-inflammatory medicines (pain medicines)
- medicines for depression or mental health problems
- laxatives
- the following medicines should be taken at least 2 hours before starting PREPOPIK® and not less than 6 hours after taking PREPOPIK®:
  - tetracycline
  - fluoroquinolone antibiotics
  - iron
  - digoxin (Lanoxin)
  - chlorpromazine
  - penicillamine (Cuprimine, Depen)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure if you are taking the medicines listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take PREPOPIK®?

See the Instructions for Use on the outer product carton for dosing. You must read, understand, and follow these instructions to take PREPOPIK® the right way.

- **Take PREPOPIK® exactly as your healthcare provider tells you to take it**. Your healthcare provider will prescribe the Split-Dosing option or the Day-Before Dosing option, depending on colonoscopy scheduling, distance traveled, and other personal circumstances.
- A complete preparation requires 2 packets of PREPOPIK® for oral solution taken separately, each followed by additional fluids.
- It is important for you to drink the additional prescribed amount of clear liquids after taking PREPOPIK to prevent fluid loss (dehydration).

- Examples of clear liquids include water, clear broth, apple juice, white cranberry juice, white grape juice, and ginger ale, plain jello (not red or purple) and frozen juice bars (not purple or red).
- Do not eat solid foods or drink milk while taking PREPOPIK®
- Drink clear liquids until your colonoscopy.
- Do not take other laxatives while taking PREPOPIK®.
- Stop drinking PREPOPIK® temporarily or allow for longer time between each dose if you have bloating, distension, or stomach (abdominal) pain until your symptoms improve.
- Stop taking PREPOPIK® and call your healthcare provider right away if you develop hives or rash after you take your first packet of PREPOPIK®. These may be signs of an allergic reaction.

See the Instructions for Use on the outer product carton for dosing. You must read, understand, and follow these instructions to take PREPOPIK® the right way.

1) Split-Dose (evening-before and day of the procedure) Dosing
Take your first packet of PREPOPIK® the night before your colonoscopy, and take your second dose the next day, in the morning before your colonoscopy.

On the day before your colonoscopy procedure – 1 packet:
• Dissolve 1 packet of powder in 5 ounces of cold water in the evening, followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before bed.

On the day of the colonoscopy procedure – 1 packet:

• Dissolve 1 packet of powder in 5 ounces of cold water in the morning (5 hours before the colonoscopy), followed by at least three 8-ounce drinks of clear liquids before the colonoscopy.

You may continue to drink clear liquids until 2 hours before the time of the colonoscopy.

2) Day-Before (afternoon and evening-before the procedure) Dosing
Take your first PREPOPIK® packet in the afternoon or early evening and take your second packet 6 hours later, the night before the colonoscopy.

On the day before the colonoscopy procedure – 2 packets:
• Dissolve 1 packet of powder in 5 ounces of cold water in the afternoon or early evening, followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before the next dose.

• Dissolve 1 packet of powder in 5 ounces of cold water in the late evening, followed by three 8-ounce drinks (upper line on the dosing cup), of clear liquids before bed.

You may continue to drink clear liquids until 2 hours before the time of the colonoscopy.

What are the possible side effects of PREPOPIK®?

PREPOPIK® can cause serious side effects, including:

See "**What is the most important information I should know about PREPOPIK®"?**
- **changes in certain blood tests**. Your healthcare provider may do blood tests after you take PREPOPIK® to check your blood for changes. Tell your healthcare provider if you have any symptoms of too much fluid loss, including:
  - Vomiting
  - Nausea
  - Bloating
  - Dizziness
  - Stomach (abdominal) cramping

- Urinate less than usual
- Trouble drinking clear liquids
- Troubles swallowing
- Seizures
- Heart problems (arrhythmia). PREPOPIK® may cause irregular heartbeats.
- Ulcers of the bowel or bowel problems (ischemic colitis). Tell your healthcare provider right away if you have severe stomach (abdominal) pain or rectal bleeding. These may be symptoms of decreased blood flow to the intestine.

The most common side effects of PREPOPIK® include:

- nausea
- headache
- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of PREPOPIK®. For more information, ask your healthcare provider or pharmacist.

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

How should I store PREPOPIK®?

• Store PREPOPIK® at room temperature, between 68 to 77°F (20 to 25°C).

Keep PREPOPIK® and all medicines out of the reach of children.

General information about the safe and effective use of PREPOPIK®.

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

This Medication Guide summarizes the most important information about PREPOPIK®. If you would like more information, talk with your healthcare provider. You can also ask your pharmacist or healthcare provider for information that is written for healthcare professionals.

For more information, go to www.ferring.com or call 1-888-337-7464.

What are the ingredients in PREPOPIK®?

Active ingredients: sodium picosulfate, magnesium oxide and anhydrous citric acid

Inactive ingredients:
potassium hydrogen carbonate, saccharin sodium, orange flavor which contains acacia gum, lactose, ascorbic acid and butylated hydroxyanisole or the cranberry flavor which contains maltodextrin, glyceryl triacetate (triacetin) and sodium octenyl succinated starch

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

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Rev. 04/2015