Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid (PREPOPIK) for Oral Solution

National Drug Monograph

June 2013

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Sodium picosulfate, magnesium oxide, and anhydrous citric acid (SPS+Mg, PREPOPIK) powder for oral solution is a low-volume, dual-acting osmotic and stimulant laxative that was approved by the U.S. Food and Drug Administration on July 16, 2012 for cleansing the colon in adults preparing for colonoscopy.[1]

- Sodium picosulfate is hydrolyzed by colonic bacteria to desacetylbisacodyl, the active metabolite of bisacodyl, while magnesium oxide and anhydrous citric acid react with water to form magnesium citrate.

- SPS+Mg is supplied in powder packets for reconstitution with cold water immediately before use. The preferred dosing regimen is the "Split Dose" method which consists of one dose administered during the evening before the colonoscopy (with at least five 8-ounce drinks of clear liquids) followed by the second dose administered on the morning of the colonoscopy (with at least three 8-ounce drinks of clear liquids). The alternative dosing regimen is the "Day Before" method which consists of one dose administered during the afternoon before the colonoscopy (with five 8-ounce drinks of clear liquids) followed by the second dose 6 hours after the first dose on the evening before the colonoscopy (with three 8-ounce drinks of clear liquids).[2,3]

- Contraindications, warnings, and precautions for SPS+Mg are similar to those for alternative bowel preparations. Electrolyte abnormalities such as hypermagnesemia have been noted in clinical studies.[2] SPS+Mg is contraindicated in patients with severely reduced renal function (creatinine clearance less than 30 mL/minute). Patients with renal insufficiency or patients taking medications that affect renal function concomitantly are at an increased risk for renal injury.[3]

- The comparative efficacy of SPS+Mg versus 2L PEG-3350 and bisacodyl tablets was established in two U.S. clinical studies. In both studies, SPS+Mg was as effective as 2L PEG-3350 and bisacodyl tablets in cleansing the colon. In the study in which SPS+Mg was administered in the Split-Dose (preferred) regimen, it was superior to the control preparation in cleansing the colon.[4,5,6,7]

- Tolerability of SPS+Mg was superior to 2L PEG-3350 and bisacodyl tablets bowel preparation kit in clinical studies.[2,6] Adverse reactions associated with SPS+Mg included nausea, vomiting, headache, and electrolyte disturbances and are similar to those of alternative bowel preparations.[2]

- Studies for off-label use of SPS+Mg have shown that it is a treatment option for constipation, barium enema, CT colonography, and flexible sigmoidoscopy. [8, 9,10,11,12,13,14,15,16,17]

- As with other bowel preparations, oral medication that is administered within 1 hour of the start of administration of SPS+Mg may be flushed from the gastrointestinal tract and the medication may not be absorbed. In addition, interactions may occur with medications that increase the risk for fluid and electrolyte disturbances, NSAIDs or other medications known to induce syndrome of inappropriate antidiuretic hormone secretion, and antibiotics which may reduce the efficacy of bowel preparation.[3,5,6,7,8,18]

Conclusion: SPS+Mg for oral solution is a low-volume, dual-mechanism colon cleansing agent that exerts its laxative action by virtue of conversion of sodium picosulfate to desacetylbisacodyl, the active moiety of the stimulant laxative bisacodyl, and the formation of the osmotic laxative magnesium citrate. Extensive data and many years of non-U.S. clinical experience support the safety and efficacy of SPS+Mg as a bowel cleanser. When administered in the Split-Dose (preferred) regimen, SPS+Mg was shown to be superior to the 2L PEG-3350 and bisacodyl tablets; however, the effect size was small. In addition, SPS+Mg demonstrated improved tolerability compared to these alternative bowel preparations. Although improved tolerability may lead to improved patient compliance with bowel preparation and therefore increased colorectal cancer (CRC) screening and survival rates,[5,6,7] this has not been evaluated with SPS+Mg.

SPS+Mg is a pregnancy category B drug. All other bowel preparations are pregnancy category C. It should be noted that SPS+Mg should not be used in renal insufficiency.[2,3]

No studies directly comparing SPS+Mg with a combination of bisacodyl tablets plus magnesium citrate in terms of colon cleansing efficacy were available; however, due to mechanism of action, the bisacodyl tablets plus magnesium citrate combination may be expected to be interchangeable with SPS+Mg at equivalent doses and have a cost advantage. Further studies are needed to confirm the therapeutic equivalence of the combination of bisacodyl tablets plus magnesium citrate to SPS+Mg.

The advantages of SPS+Mg are offset by the non-contract drug acquisition cost that is 2 to 750 times higher than alternative bowel preparation agents.

Introduction

Sodium picosulfate, magnesium oxide, and anhydrous citric acid (SPS+Mg, PREPOPIK™, Ferring Pharmaceuticals) for oral solution is a low volume dual-acting osmotic and stimulant laxative that was approved by the U.S. Food and Drug Administration on July 16, 2012 for cleansing the colon in adults preparing for colonoscopy.[1] There are other low-volume dual-acting bowel preparations on the market such as HalfLytely™ (2L polyethylene glycol 3350; electrolytes and bisacodyl tablets). With 2L polyethylene glycol 3350; electrolytes and bisacodyl tablets, the powder preparation is dissolved in 2 liters (67.6 ounces) of water and consumed. The proposed benefit of SPS+Mg is that the powder preparation is only dissolved in 5 oz of water at two different times and supplemented with 40 ounces then 24 ounces of a clear liquid of choice.

In 2012, colorectal cancer ranked third in terms of the number of new cases of cancer and was the third leading cause of cancer deaths among men and women despite having a high survival rate with early detection.[19] Screening colonoscopy is recommended in the general population every 10 years beginning at age 50 and in African American adults beginning at age 45.[2] More frequent screening is recommended when polyps or other abnormalities are found.

Patient compliance with screening recommendations for colorectal cancer remains low, in part because of difficulties with bowel preparation methods for colonoscopy.[2] Many patients cannot finish the relatively large volume (2–4 liters) of bowel preparation solution that is recommended, and reluctance to undergo bowel preparation remains a major deterrent for patients. Compliance could potentially be enhanced by improving the taste, decreasing the volume of bowel preparation solutions, and using a split-dose regimen. In a split-dose regimen, one-half to three-fourths of the product is administered on the day before the colonoscopy and the remainder on the day of the procedure. Better tolerability and improved visibility during colonoscopy have been noted with the split-dosing approach.[2,6,7,20] Inadequate colon cleansing can lead to longer procedures, failed colonoscopy attempts and need for repeat colonoscopies, and increase the cost of colonoscopy.

The American Society for Gastrointestinal Endoscopy consensus document on bowel preparation for colonoscopy and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines were reviewed for recommendations on bowel preparations. Both of these documents were last updated prior to approval of sodium picosulfate, magnesium oxide and citric acid on July 16, 2012. The European product Picolax (sodium picosulfate, magnesium oxide and citric acid) was found to be equally effective in terms of quality of preparation and more tolerable when compared with PEG. Conflicting results have been seen in comparisons between sodium phosphate and Picolax (sodium picosulfate, magnesium oxide and citric acid).[21] There is recommendation that sodium picosulphate preparations be used with caution in patients at risk of, or suffering from, hypervolemia, including those patients taking high-dose diuretics, those with congestive cardiac failure and advanced cirrhosis, and those with chronic kidney disease (evidence: grade 1C).[22]

A systematic review/meta-analysis showed that a split-dose 4-L PEG bowel regimen was superior to other types of bowel preparations, and suggested that it be the standard to which other regimens are compared.[23]

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating SPS+Mg for oral solution for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

SPS+Mg is a dual-acting stimulant and osmotic laxative. Sodium picosulfate, a prodrug, is hydrolyzed by bacteria in the colon to form an active metabolite, desacetylbisacodyl (bis-[p-hydroxy-phenyl]-pyridyl-2-methane, BHPM), which acts directly on the colonic mucosa to stimulate peristalsis. Desacetylbisacodyl, the active metabolite of bisacodyl, is water insoluble and minimally absorbed from the gastrointestinal tract. Desacetylbisacodyl / BHPM is responsible for the laxative action of both sodium picosulfate and bisacodyl.

No studies directly comparing SPS+Mg and bisacodyl tablets plus magnesium citrate in terms of colon cleansing efficacy were found; however, the bisacodyl tablets plus magnesium citrate combination may be expected to be interchangeable with SPS+Mg at equivalent doses. To achieve complete evacuation of the intestine, the recommended adult dosage of bisacodyl is two to four coated tablets the night before the examination (up to 30 mg), followed by one suppository in the morning of the examination. A dose of two 5-mg bisacodyl tablets is considered to be the dosage equivalence to one packet of SPS+Mg powder. It is recommended that bisacodyl that is used for preparation of diagnostic procedures be used under medical

supervision.[24] Pharmacokinetic equivalencies are difficult to assess due to lack of information in the package insert.

A chemical reaction among magnesium oxide, citric acid and water creates the osmotic agent magnesium citrate, which causes water to be retained within the gastrointestinal tract.[2,3,4] The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a purgative effect which, when SPS+Mg is ingested with additional fluids, produces watery diarrhea.

The onsets of action of SPS and bisacodyl are 6 to 12 hours, but when combined with magnesium citrate, the onset of action can be as short as 0.5 hours.

Sodium picosulfate, magnesium oxide and anhydrous citric acid are excreted in the urine. The fraction of the absorbed sodium picosulfate dose excreted unchanged in urine is 0.19%. Thirteen out of 16 study subjects had plasma BHPM concentrations below the lower limit of quantification (0.1 ng/mL). After administration of 2 packets of SPS+Mg separated by 6 hours, sodium picosulfate reached a mean Cmax of 3.2 ng/mL at approximately 7 hours. The half-life of sodium picosulfate is 7.4 hours. Baseline uncorrected magnesium concentration reached a Cmax of approximately 1.9 mEq/L at 10 hours and represented an increase of approximately 20% from the baseline.[2,3,4]

In vitro studies have shown that sodium picosulfate did not inhibit the major CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) and is not an inducer of CYP1A2, CYP2B6 or CYP3A4/5.[2,3,4]

Synonyms and Similar Foreign Products

SPS+Mg or similar products have been available in non-U.S. countries for years. Those that have been studied are described in Table 1.

Table 1: Foreign Products Containing SPS+Mg Powder for Oral Solution

Trade Name	Company	Country	Ingredients	Strength (mg / g / g)
PICO-SALAX	Ferring Pharmaceuticals	Canada	SPS+Mg	10 / 3.5 / 12
PURG-ODAN	Odan Laboratories	Canada	SPS+Mg	10 / 3.5 / 12
PICOSALAX	Pharmaco (NZ)	New Zealand	SPS+Mg	10 / 3.5 / 12
PICOLAX	Ferring Pharmaceuticals	U.K.	SPS+Mg	10 / 3.5 / 12
PICOPREP-3™	Pharmatel Fresenius Kabi Pty Ltd, Pymble	Australia	SPS+Mg, aspartame	10 / 3.5 / 12

SPS+Mg, Sodium picosulfate, magnesium oxide, citric acid;

The combination of SPS+Mg can also be achieved by combining sodium picosulfate with magnesium citrate.

FDA Approved Indication(s)

SPS+Mg (PREPOPIK) for oral solution was approved in July 2012 for cleansing of the colon as a preparation for colonoscopy in adults.[1,2,3]

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

SPS+Mg has been studied for potential off-label uses including barium enema and constipation.[8,9,10,11,12,13,14,15,16,17]

Barium enema

- In an evaluator-blinded randomized clinical trial comparing three products—the conventional cleansing enema, Pico-salax, and Golytely—for barium enema bowel preparation, there was no significant difference in the efficacy (bowel cleanliness and barium coating) between the three regimens. The use of Pico-salax resulted in the most bowel openings compared to the cleansing enema and Golytely, however, Pico-salax was only significantly better than the cleansing enema. Pico-salax was shown to have significantly less vomiting when compared to Golytely and significantly less abdominal fullness when compared to the cleansing enema and Golytely. When compared to Pico-salax, Golytely was less acceptable in taste and amount of fluid intake.[8]

- In a study comparing Picolax, Picolax with cleansing enema, and Citramag, all three treatments were equally tolerated. The quality of the bowel evacuation was significantly poorer in the cleansing enema group ($P < 0.01$) and significantly better in the Picolax alone group ($P < 0.01$).[9]

- A comparison of Fleet Phospho-soda with Picolax showed no difference in fecal residue or in the bowel coating;, however, patients found Picolax to be significantly easier to take for reasons including better taste, less nausea, and less vomiting ($P < 0.01$).[10]

- A study comparing magnesium citrate to Picolax revealed that normal daily activities were inconvenienced significantly more by Picolax ($P < 0.01$) but that magnesium citrate caused significantly more interruption of sleep ($P < 0.01$) and more fecal residue and poorer overall bowel preparation ($P < 0.01$).[11]

- In a prospective, randomized three-arm trial comparing Picolax, Picolax following a 3-day low-residue diet, and Kleen-Prep (a polyethylene-glycol osmotic agent), the low residue diet added no benefit to Picolax preparation, which was adequate in 80% of patients. The Kleen-Prep arm failed to achieve adequate preparation in 46% of patients and caused increased nausea, abdominal bloating, and pain ($P < 0.01$).[12]

Constipation

- Results from a pilot study on the efficacy of one half of a sachet of Picolax given every other day three times a week as a treatment for refractory constipation showed that the mean number of weekly complete spontaneous bowel movements increased from 0.5 to 2.4 times per week ($P = 0.02$). The ratio of patients who took rescue medication decreased significantly from 73% to 0% ($P = 0.008$).[13]

- Analysis of primary and secondary efficacy parameters indicated that, for a laxative effect in chronic constipation, bisacodyl and sodium picosulphate are equally effective at similar doses. Though both treatments were associated with more than a doubling of stool frequency from baseline values and a change in average stool consistency from 'moderately

hard'/'hard', to 'soft'/'well-formed', the change in mean number of stools from baseline was slightly greater in the sodium picosulphate group.[25]

CT Colonography

- Patients who were treated with Picolax retained significantly less fluid (P <0.0001) when compared with Citramag (magnesium carbonate 11.57 g and citric acid 17.79 g powder per sachet for oral solution, U.K.) for all segments combined. There was significantly more retained solid residue with Picolax (P =0.002) when compared to Citramag. The authors concluded that Picolax is a more suitable preparation for CT colonography than Citramag.[14]

Flexible Sigmoidoscopy

- A randomized controlled trial comparing Picolax to Klyx enemas (docusate sodium 240mg and sorbital 60g in 240mL) for flexible sigmoidoscopy found that there was no difference in efficacy between the two preparations, however, patients preferred Picolax.[15]

- A single blind, randomized trial comparing efficacy and acceptability of a single sachet of oral Picolax to a single phosphate enema for flexible sigmoidoscopy found that compliance with the single enema (84%) was higher than compliance with single sachet of Picolax (79%), that sleep disturbances were more frequent in the Picolax group, that 30% found the diet restriction required by Picolax to be difficult, and that the quality of preparation was better with the single enema than with one single sachet of Picolax.[16]

- In a randomized, controlled clinical trial comparing one sachet of oral sodium picosulphate and magnesium citrate powder for oral solution to a self-administered phosphate enema, the enema proved to be superior to sodium picosulphate and magnesium citrate in terms of bowel preparation for flexible sigmoidoscopy and incidence of associated adverse symptoms. Approximately 93% of bowel preparations were rated as adequate or better in the enema group as opposed to 74% in the sodium picosulphate and magnesium citrate group. Adverse symptoms occurred in 20% of patients using the enema and 52% of patients taking the sodium picosulphate and magnesium citrate.[17]

Current VA National Formulary Alternatives

The following items are formulary alternatives to SPS+Mg for bowel cleansing prior to colonoscopy:

- Polyethylene glycol 3350 powder 255g and bisacodyl 5mg tablet bowel prep
- HalfLytely™ (2L polyethylene glycol; bisacodyl; electrolytes)
- GoLytely™ (4L polyethylene glycol 3350; electrolytes)
- Bisacodyl TAB, EC plus magnesium citrate LIQUID, ORAL

Dosage and Administration

SPS+Mg is supplied as powder for reconstitution (2 packets per box). 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 16.1 grams of powder. The contents of both packets constitute a complete bowel cleansing regimen. The powder must be reconstituted with cold water immediately before use and should not be prepared in advance. Directions for reconstitution of SPS+Mg powder are as follows:[2,3]

- Fill the supplied dosing cup with cold water up to the lower (5-ounce or 0.15 L) line on the cup and add in the contents of one packet of SPS+Mg powder.
- Stir for 2 to 3 minutes. The reconstituted solution may become slightly warm as the powder dissolves.
- Administer after reconstitution

There are two dosing regimens for the provider to consider based on colonoscopy scheduling, distance traveled, and other personal situations. Both regimens require administration of the medication at two separate dosing times:[26]

- The preferred dosing regimen is the "Split Dose" method which consists of two separate doses:
  - The first dose is administered during the evening before the colonoscopy (5:00 to 9:00 PM) followed by five 8-ounce drinks (upper line on the dosing cup) of clear liquids before bed. The clear liquids should be consumed within 5 hours of taking the first dose.
  - The second dose is administered the next day, on the morning of the colonoscopy, and is followed by at least three 8-ounce drinks of clear liquids. Again, the clear liquids should be consumed within 5 hours of the second dose and can be taken up until 2 hour before the time of the colonoscopy.
- The alternative dosing regimen is the "Day Before" method and it also consists of two separate doses:
  - The first dose is administered during the afternoon or early evening (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 (within 5 hours).
  - The second dose is administered 6 hours after the first dose (10:00 PM to 12:00 AM) on the evening before the colonoscopy followed by three 8-ounce drinks of clear liquids before bed (within 5 hours).

Additional dosing information includes the following[2,3]:

- Take the SPS+Mg Split-dosing or Day-before regimen exactly as instructed.
- A complete preparation requires 2 packets of SPS+Mg for oral solution taken separately and each followed by additional fluids as instructed.
- It is important to drink the additional prescribed amount of clear liquids after taking SPS+Mg to prevent 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 SPS+Mg.
- Do not take other laxatives while taking SPS+Mg.
- If bloating, distension, or stomach (abdominal) pain occur, temporarily stop taking or delay the second dose until the symptoms resolve and contact your healthcare provider.
- Stop taking sodium picosulfate, magnesium oxide and anhydrous citric acid SPS+Mg, and call the healthcare provider immediately if rash or hives appear after taking the first packet of powder as these could be signs of an allergic reaction.

Special considerations:[2,3]

- Because this is a magnesium-containing bowel preparation, caution should be used when prescribing SPS+Mg for patients with renal impairment or for patients who are taking medications that affect renal function.
  - To prevent risk of renal injury, adequate hydration before, during and after the use of SPS+Mg should be emphasized.
  - In patients with a creatinine clearance of less than 30 mL/min, accumulation of magnesium in the plasma could occur and the use of SPS+Mg should be avoided.
- No pharmacogenomics information is available at this time.

The total volume of fluid recommended, including the 0.30 L (two 0.15-L doses) of diluted SPS+Mg fluid and 1.92 L of subsequent clear liquids, is about 2.22 L (1.35 L for the first dose and 0.87 L for the second dose of SPS+Mg). This volume is slightly more than that taken with HalfLytely (2L polyethylene glycol 3350; electrolytes and bisacodyl tablets) powder, which is dissolved in 2 L of water.

Efficacy

The consensus guidelines for the prescription and administration of oral bowel cleansing agents, produced by the British Society of Gastroenterology, state that sodium picosulphate and magnesium citrate produces the 'driest' bowel with the lowest amount of watery residue when compared to Citramag and PEG preparations. The same guidelines advise that sodium picosulphate and magnesium citrate could be potentially advantageous for radiological investigation.[27]

Evaluation of the colon-cleansing efficacy of SPS+Mg was assessed in 2 randomized, investigator-blinded, active-controlled, multicenter US trials for non-inferiority against the comparator 2 L of PEG-3350 and bisacodyl tablets. One trial evaluated a split-dose regimen and the other trial, a day-before regimen. These trials were conducted in 1,211 patients scheduled to undergo elective colonoscopy.[5,6,7]

Efficacy Measures

Responders on Aronchick Scale[2]: The primary efficacy endpoints in both pivotal trials were the proportion of patients with successful colon cleansing using the Aronchick Scale as assessed by blinded colonoscopists. Responders were defined as patients with an "excellent" or "good" rating on the Aronchick Scale.

Table 2: Aronchick Scale

Grade	Description
Excellent	> 90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization
Good	> 90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	> 90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	< 90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

Responders on Ottawa Scale (cleanliness)**Error! Reference source not found.**: The secondary efficacy variables in both pivotal trials used the Ottawa Scale to assess colon cleansing by colon segments. Responders for cleansing of the colon segments were defined as a rating of "excellent," "good," or "fair" on the Ottawa Scale.

Table 3: Ottawa Scale

Grade	Description
0	Excellent: Mucosal detail clearly visible. If fluid is present, it is clear. Almost no stool residue.
1	Good: Some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary
2	Fair: Turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary.
3	Poor: Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained.
4	Inadequate: Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

Satisfaction and Tolerability: Measured by the Subject Acceptability and Tolerability Questionnaire given to patients in the FE2009-01 and FE2009-02 trials.

Dosing Regimens

Split-dose Regimen: the first packetful of SPS+Mg powder dissolved in 5 ounces of water is taken the evening before colonoscopy (between 5:00-9:00PM) followed by five 8-ounce glasses of clear liquid and the second packetful the morning of colonoscopy (5 hours prior to but not more than 9 hours prior to colonoscopy) followed by three 8-ounce glasses of clear liquid.

Day-before Regimen: Both SPS+Mg packetfuls are taken separately the day before colonoscopy; the first packet taken in the afternoon (between 4:00-6:00PM) followed by five-8 ounce glasses of clear liquid and the second packet taken in the late evening (6 hours later between 10:00 PM-12:00 AM) followed by three 8-ounce glasses of clear liquid.

Summary of Efficacy Findings

- A total of 604 patients were enrolled, randomized, and received either split-dosed SPS+Mg or 2 L of PEG-3350 in a phase 3 study investigating the efficacy, safety, and tolerability of each bowel preparation.
- Split-Dosing of SPS+Mg was superior to 2 L of PEG-3350 and bisacodyl tablets as measured by the Aronchick scale for overall cleansing of the colon, and by the Ottawa Scale for cleansing of the ascending, mid, and recto-sigmoid. The effect size for overall colon cleansing was relatively small (absolute difference of 9.8%) with an NNT (95% CI) of 11 (6–40).

- A total of 598 patients were enrolled, randomized, and received either day-before dosed SPS+Mg or 2 L of PEG-2250 in a phase 3 study investigating the efficacy, safety, and tolerability of each bowel preparation.

- Day-Before dosing of SPS+Mg was non-inferior to 2 L of PEG-3350 and bisacodyl tablets as measured by the Aronchick scale for overall cleansing of the colon, and by the Ottawa Scale for cleansing of the ascending, mid, and recto-sigmoid colon.

Table 4: Summary of SPS+Mg Trials Supporting FDA Approval

<table>
<tr><th>Trial / Quality</th><th>Study Treatments</th><th>Design</th><th>Results</th></tr>
<tr>
<td>Data on File FE2009-01.

Quality: Fair</td>
<td>“Split-dose”

SPS+Mg 10mg-3.5g-12g powder for solution 1 packet + 40 fluid ounces of liquid day before colonoscopy, and 1 packet + 24 fluid ounces of liquid day of colonoscopy

PEG-3350 2 L + electrolytes solution and two 5-mg bisacodyl tablets given day before colonoscopy</td>
<td>Randomized, investigator-blinded, active-controlled, non-inferiority, multicenter US trial

ITT (N = 304 vs. 297)
PP (N = 277 vs. 274)

Margin of noninferiority: Not reported</td>
<td>Responder Rates
<table>
<tr><th></th><th>SPS+Mg</th><th>PEG+BIS*</th><th>Treatment Difference</th><th>1-sided 97.5% CI</th></tr>
<tr><td>ITT</td><td>256 (84.2%)</td><td>221 (74.4%)</td><td>9.8%</td><td>3.4</td></tr>
<tr><td>PP</td><td>235 (84.8%)</td><td>207 (75.5%)</td><td>9.3%</td><td>2.7</td></tr>
</table>
Responders = excellent or good rating on Aronchick Scale

Primary endpoint (Aronchick scale): The lower bound of the 1-sided 97.5% confidence interval for the treatment difference was 3.4% in the ITT analysis set and 2.7% in the PP analysis set, satisfying criteria for noninferiority. The lower bound of the confidence interval was > 0%, thus establishing superiority of SPS+Mg in bowel cleansing.

Secondary endpoint (Ottawa Scale): In both ITT and PP analysis sets, the noninferiority of SPS+Mg compared with 2L PEG-3350 and bisacodyl tablets in cleansing of the ascending, mid, and recto-sigmoid colon was established. The lower bound of the confidence interval was > 0%, thus establishing superiority of SPS+Mg in bowel cleansing of the ascending colon, mid colon, and recto-sigmoid colon in the ITT analysis, and the ascending and mid colon in the PP analysis. The superiority of SPS+Mg vs. 2L PEG-3350 and bisacodyl tablets was established for overall colon cleansing of the 3 colon sections – ascending, mid, and recto-sigmoid, in the ITT analysis set.

Secondary endpoint (Subject Acceptability and Tolerability Questionnaire): SPS+Mg was statistically significantly superior to 2L PEG-3350 and bisacodyl tablets based on subject ratings on all questions (P<0.001). For further data, see Tolerability section below.</td>
</tr>
</table>

<table>
<tr><th>Trial / Quality</th><th>Study Treatments</th><th>Design</th><th>Results</th></tr>
<tr>
<td>FE2009-02

Quality: Fair

Katz PO, Rex DK, Epstein M, Grandhi NK, Vanner S, et al. A dual-action, low-volume bowel cleanser administered the day before colonoscopy: results from the SEE CLEAR II study. Am J Gastroenterol. 2013; 108:401-409.</td>
<td>“”Day Before”

Prepopik™10mg-3.5g-12g powder for solution 2 packets + total of 64 fluid ounces of liquid day before colonoscopy in divided doses

PEG 2 L + two 5-mg bisacodyl tablets given day before colonoscopy</td>
<td>Randomized, investigator-blinded, active-controlled, non-inferiority, multicenter US trial

ITT N = 294 vs. 260

PP N = 260 vs. 280

Margin of noninferiority: 9%</td>
<td>
<table>
<tr><th></th><th>Prepopik™</th><th>PEG+BIS*</th><th>Treatment Difference</th><th>1-sided 97.5% CI</th></tr>
<tr><td>ITT</td><td>244 (83.0%)</td><td>239 (79.7%)</td><td>3.3%</td><td>- 2.9</td></tr>
<tr><td>PP</td><td>216 (83.1%)</td><td>222 (79.3%)</td><td>3.8%</td><td>- 2.8</td></tr>
</table>
Responders = excellent or good rating using Aronchick Scale

Primary endpoint (Aronchick scale): The lower bound of the 1-sided 97.5% confidence interval for the treatment difference was -2.9% in the ITT analysis set and -2.8% in the PP analysis set, demonstrating noninferiority of SPS+Mg to 2 L of PEG-3350 and bisacodyl tablets in both sets. However, the lower bound of the confidence interval was not > 0% and therefore superiority of SPS+Mg to 2L PEG-3350 and bisacodyl tablets was not established.

Secondary endpoint (Ottawa Scale): In the ITT analysis set, the noninferiority of SPS+Mg compared to 2L PEG-3350 and bisacodyl tablets in overall colon cleansing and cleansing of the ascending, mid, and recto-sigmoid colon separately, was demonstrated.

Secondary endpoint (Subject Acceptability and Tolerability Questionnaire): SPS+Mg was statistically significantly superior to 2L PEG-3350 and bisacodyl tablets based on subject ratings on all questions (P<0.0001). For furthers data, see Tolerability section below.
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*PEG + BIS, PEG 2 L + two 5mg bisacodyl tablets

Appendix: Clinical Trials (page 23).

Safety

SPS+Mg has been available for nearly 30 years outside of the U.S. with over 20 million doses being administered.

Deaths and Other Serious Adverse Events

The incidence of serious treatment-emergent adverse events (TEAEs) was 0.3% in the SPS+Mg group and 0.7% in the 2L PEG-3350 plus bisacodyl tablets group.

Common Adverse Events

After administration of SPS+Mg, gastrointestinal adverse reactions, including abdominal bloating, distension, abdominal pain/cramping, fecal urgency, and watery diarrhea are expected. During clinical trials, only gastrointestinal events that required medical intervention and met criteria for serious adverse events were specifically noted. The most common treatment-emergent adverse reactions reported during clinical trials in adult patients receiving either Split-Dose or Day-Before regimens are listed below in Table 5.[5,6,7,18]

Table 5: Treatment-Emergent Adverse Events observed in > 1% of Patients using the Split-Dose Regimen and Day-Before Regimen*

	Study 1: Split-Dose Regimen		Study 2: Day-Before Regimen	
Adverse Events	SPS+Mg (N=305) n (% = n/N)	2L PEG-3350 and bisacodyl tablets (N=298) n (% = n/N)	SPS+Mg (N=296) n (% = n/N)	2L PEG-3350 and 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 (1.6)	10 (3.4)	4 (1.4)	6 (2.0)

* Abdominal bloating, distension, pain/cramping, and watery diarrhea not requiring an intervention were not tabulated.

Orthostatic changes on the day of colonoscopy occurred in approximately 20% of patients in both SPS+Mg and 2L PEG-3340 and bisacodyl tablet arms during clinical trials of SPS+Mg. SPS+Mg was associated with numerically higher rates of abnormal electrolyte shifts and lower rates of high creatinine when compared to 2L of PEG + electrolytes plus two x 5-mg bisacodyl tablets as shown in Table 6.

Table 6: Electrolyte Shifts from Normal Baseline to Outside the Normal Range

Laboratory Parameter (direction of change)	Visit	Study 1: Spilt-Dose Regimen		Study 2: Day-Before Regimen	
		Sodium picosulfate, magnesium oxide, and anhydrous citric acid	2L PEG-3350 and bisacodyl tablets	Sodium picosulfate, magnesium oxide, and anhydrous citric acid	2L PEG-3350 and 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)	0/297 (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 (0.4)
	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	22/201 (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)

Other Adverse Events

Other adverse events are further outlined in Table 7 below. [2]

Table 7: Other adverse events

	SPS+Mg	2L PEG-3350 and bisacodyl tablets
Withdrawals due to AEs	0%	0.3%
TEAEs considered to be possibly or probably related to study drug	6.2%	8.7%
Treatment-emergent AEs	69.2%	72.8%
Diverticulum	19.7%	24.2%
Colon Adenoma	18.4%	17.1%
Hemorrhoids	17.7%	19.8%
Colonic Polyp	17.0%	17.1%
Chills	0%	1.0%
Abnormal Urine pH	23.4%*	7.6%

* Likely related to elevated magnesium excretion; results returned to normal within 24-48 hours post-procedure

Mucosal inflammation has also been associated with sodium picosulfate.[28]

Tolerability

SPS+Mg was statistically superior (P<0.001) to 2L PEG-3350 and bisacodyl tablets on all questions on the Subject Acceptability and Tolerability Questionnaire including tolerability and satisfaction ratings.[2]

Table 8: Combined Scores from Key Clinical Studies for Subject Acceptability and Tolerability Questionnaire: Satisfaction Items[29]

Item	SPS+Mg	2L PEG-3350 and bisacodyl tablets
Rated the bowel preparation as easy or very easy to consume	88.4%*	33.2%
Able to consume the entire preparation	99.3%*	90.9%
Overall experience rated as excellent	46.2%*	17.8%
Taste of the preparation rated good or excellent	73.8%*	24.7%

*p<0.0001 for SPS+Mg vs 2L PEG-3350 and bisacodyl tablets

Appendix: Clinical Trials (page 23).

Contraindications

SPS+Mg is contraindicated in the following conditions[3]:

- Patients with severely reduced renal function (creatinine clearance less than 30 mL/minute) which may result in accumulation of magnesium
- Gastrointestinal obstruction or ileus (including gastrointestinal obstruction, retention, or perforation)
- Bowel perforation
- Toxic colitis or toxic megacolon
- Gastric retention
- An allergy to any of the ingredients in SPS+Mg.

Use caution, encourage adequate hydration before, during, and after the use of SPS+Mg and perform baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in patients with[2,3]:

- Severe active ulcerative colitis
- Patients with impaired renal function
- Patients who are taking concomitant medications that could affect renal function or increase the risk of renal injury, including but not limited to:
  - Diuretics
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptor blockers
  - Non-steroidal anti-inflammatory drugs

The safety and efficacy of SPS+Mg solution in neonates, infants, children, and adolescents have not been established.

Warnings and Precautions

Common warnings and precautions are outlined below.[2,3]

Serious Fluid and Serum Chemistry Abnormalities

Serious adverse events including cardiac arrhythmias, seizures, and renal impairment can occur in patients taking SPS+Mg due to fluid and electrolyte disturbances. Any pre-existing fluid or electrolyte abnormalities should be corrected before SPS+Mg is initiated. Patients should be encouraged to adequately hydrate before, during, and after the use of SPS+Mg, and laboratory assessments should be completed prior to initiation. Approximately 20% of patients had orthostatic changes on the day of colonoscopy. If significant vomiting or signs of dehydration including orthostatic hypotension occur after taking SPS+Mg, post-colonoscopy lab tests including electrolytes, creatinine, and BUN should be completed.

Seizures

Generalized tonic-clonic seizures have been reported, especially in patients taking medications that lower the seizure threshold, patients withdrawing from alcohol or benzodiazepines, and patients with electrolyte abnormalities. It is recommended to ensure adequate hydration before, during, and after the use of SPS+Mg to prevent electrolyte abnormalities and seizures.

Use in Patients with Renal Impairment

Patients with renal insufficiency and patients who are taking medications that affect renal function could be at increased risk of renal injury from SPS+Mg. Baseline and post-colonoscopy testing including electrolytes, creatinine, creatinine clearance, and BUN should occur. When creatinine clearance is < 30 mL/min, accumulation of magnesium in the plasma can occur.

Cardiac Arrhythmias

Rare but serious arrhythmias associated with the use of osmotic laxative products for bowel preparation have been reported. Pre- and post-colonoscopy EKGs may be considered in patients who are at increased risk for these serious cardiac arrhythmias including patients with prolonged QT, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy.

Colonic Mucosal Ulceration, Ischemic Colitis and Ulcerative Colitis

The use of SPS+Mg along with any other stimulant laxative can increase the risk of colonic mucosal ulcerations, ischemic colitis, and ulcerative colitis especially in patients with known or suspected inflammatory bowel disease.

Use in Patients with Significant Gastrointestinal Disease

If suspected, diagnostic studies should be completed to rule out gastrointestinal obstruction or perforation before using SPS+Mg.

Aspiration

Patients with an impaired gag reflex and patients who often regurgitate should be observed during the administration of SPS+Mg to prevent aspiration.

Not for Direct Ingestion

SPS+Mg powder should not be ingested undissolved as this could increase the risk of electrolyte disturbances, dehydration, nausea, and vomiting.

Special Populations

Special populations that have been identified are outlined below.[2,3]

Pregnancy

SPS+Mg is in pregnancy category B. No adequate, well-controlled studies in pregnant women have been completed; therefore, SPS+Mg should only be used in pregnant women if clearly needed. PEG solutions, in pregnancy category C, have been used in pregnant women.

Nursing Mothers

It is unknown whether SPS+Mg is excreted in human milk. Caution should be used when SPS+Mg is administered to a nursing woman.

Pediatric Patients

The safety and efficacy of SPS+Mg has not been evaluated in pediatric patients.

Geriatric Patients

In controlled clinical trials with SPS+Mg, patients ≥ 65 years of age had a similar overall incidence of treatment-emergent adverse events as compared with patients < 65 years (73% vs. 71%). When SPS+Mg was compared with comparator agent in patients ≥ 65 years of age, to the

same, the proportion of patients with successful colon cleansing was greater in the SPS+Mg group (81.1% vs. 70.9%).

Renal Insufficiency

To prevent the risk of renal injury, adequate hydration before, during, and after the use of SPS+Mg should be recommended to patients with impaired renal function and patients taking medications that may affect renal function. Providers should perform pre- and post-colonoscopy laboratory tests to monitor electrolytes, creatinine, and BUN in these patients. In addition, patients with CrCl < 30mL/minute are at an increased risk of magnesium accumulation and should not be given SPS+Mg.

Postmarketing Safety Experience

Foreign spontaneous adverse event reports have been identified during use of formulations similar to SPS+Mg.[2,3]

Allergic reactions: rash, urticarial, and purpura.

Electrolyte abnormalities: Hypokalemia, hyponatremia, and hypermagnesemia.

Gastrointestinal issues: Abdominal pain, diarrhea, fecal incontinence, proctalgia, reversible aphthoid ileal ulcers, and ischemic colitis.

Neurologic issues: Generalized tonic-clonic seizures with and without hyponatremia in epileptic patients.

Sentinel Events

No data.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 9: Look-alike Sound-alike Names

NME Drug Name	Lexi-Comp	First Data Bank	ISMP	Clinical Judgement
Sodium Picosulfate, Magnesium Oxide, and Citric Acid	None	None	None	Sodium Sulfate, Potassium Sulfate, and Magnesium Sulfate (Suprep®) Magnesium Citrate
Prepopik™	None	None	None	Prepidil® Pristiq®

Drug Interactions

Drug-Drug Interactions

Drugs that may increase risks of fluid and electrolyte abnormalities: Use caution when prescribing SPS+Mg in patients receiving mediations or with conditions that increase the risk for fluid and electrolyte disturbances or that may increase the risk of seizure, arrhythmia, and prolonged QT in the setting of fluid and electrolyte abnormalities. In addition, use caution in patients receiving medications which may be associated with hypokalemia or hyponatremia, including medications such as diuretics, corticosteroids, cardiac glycosides. Nonsteroidal anti-inflammatory drugs (NSAIDs) or tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), antipsychotic drugs, and carbamazepine, which are medications known to induce Antidiuretic Hormone Secretion (SIAD), may increase the risk of water retention and/or electrolyte imbalance.

Potential for altered drug absorption: Oral medications administered within one hour of the start of administration of SPS+Mg may be flushed from the GI tract before that medication can be absorbed. Tetracycline, fluoroquinolone antibiotics, iron salts, digoxin, chlorpromazine, and penicillamine should be taken at least two hours before and at least six hours after administration of SPS+Mg to avoid chelation with magnesium.[2,18]

Antibiotics: Prior or concomitant use of antibiotics with SPS+Mg may reduce the efficacy of the bowel preparation since the conversion of sodium picosulfate to its active metabolite BHPM is mediated by colonic bacteria. Do not schedule a colonoscopy right after or during therapy with antibiotics, including aminoglycosides, carbacephems, carbapenems, cephalosporins, chloramphenicol, clindamycin, glycopeptides, glycylcyclines, ketolides, lincomycin, lipopeptides, macrolides, metronidazole, monobactams, oxazolidinones, penicillins, polymyxins, quinolones, streptogramins, sulfonamides, and trimethoprim.[2,18]

Drug-Food Interactions

No data.

Drug-Lab Interactions

No data.

Acquisition Costs

Please refer to the last page for VA drug acquisition costs. Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Pharmacoeconomic Analysis

No VA-relevant studies were found.

A budget-impact model for colonoscopy cost calculation and comparison was designed for multiple bowel preparation products. As a result of this model, it was determined that the main cost drivers in colonoscopies are the procedure costs and costs for inpatient stays, rather than actual drug acquisition costs of the bowel preparation products.[30]

Conclusions

SPS+Mg for oral solution is a low-volume, dual-mechanism colon cleansing agent that exerts its laxative action by virtue of conversion of sodium picosulfate to desacetylbisacodyl, the active moiety of the stimulant laxative bisacodyl, and the formation of the osmotic laxative magnesium citrate. Extensive data and many years of non-U.S. clinical experience support the safety and efficacy of SPS+Mg as a bowel cleanser. When administered in the Split-Dose (preferred) regimen, SPS+Mg was shown to be superior to the 2L PEG-3350 and bisacodyl tablets; however, the effect size was small. In addition, SPS+Mg demonstrated improved tolerability compared to these alternative bowel preparations. Although improved tolerability may lead to improved patient compliance with bowel preparation and therefore increased colorectal cancer (CRC) screening and survival rates,[5,6,7] this has not been evaluated with SPS+Mg.

SPS+Mg is a pregnancy category B drug. All other bowel preparations are pregnancy category C. It should be noted that SPS+Mg should not be used in renal insufficiency.[2,3]

No studies directly comparing SPS+Mg with a combination of bisacodyl tablets plus magnesium citrate in terms of colon cleansing efficacy were available; however, due to mechanism of action, the bisacodyl tablets plus magnesium citrate combination may be expected to be interchangeable with SPS+Mg at equivalent doses and have a cost advantage. Further studies are needed to confirm the therapeutic equivalence of the combination of bisacodyl tablets plus magnesium citrate to SPS+Mg.

The advantages of SPS+Mg are offset by the non-contract drug acquisition cost that is 2 to 750 times higher than alternative bowel preparation agents.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to April 2013) using the search terms <sodium picosulfate, magnesium oxide and citric acid > or <Prepopik>. The search was limited to active-controlled studies performed in humans and published in English language. Trials evaluating Pico-salax, Picoprep, or Picolax (additional trade names marketed in Canada, the United Kingdom and other countries) were included. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included. A total of 3 active controlled trials including 3 head-to-head trials were included in the evaluation.

Pivotal Studies

<table>
<tr><th>Citation
Design
Analysis type
Setting</th><th>Eligibility Criteria</th><th>Interventions</th><th>Patient Population Profile</th><th>Efficacy Results</th><th>Safety Results</th><th>Author's conclusions (optional)

Critique (optional)</th></tr>
<tr>
<td>Katz (2013)[5]

Phase 3, randomized, multicenter, assessor-blinded, non-inferiority, head-to-head study in an outpatient setting

JADAD: 3</td>
<td>Inclusion Criteria:
Age 18-80 years

At least 3 spontaneous bowel movements per week for 1 month before scheduled elective colonoscopy

Exclusion Criteria:
Acute surgical abdominal conditions; active inflammatory bowel disease; or colon disease Gastrointestinal disorders

Uncontrolled angina and/or myocardial infarction within last 3 months, congestive heart failure or uncontrolled hypertension, renal insufficiency</td>
<td>SPS+Mg

2L PEG-3350 and bisacodyl tablets

Tx taken day before colonoscopy</td>
<td>Mean age 56.8 – 56.3 years; male 35.1 – 37.4%; white 92.6 – 88.7% (SPS+Mg – 2L PEG-3350 and bisacodyl tablets)</td>
<td>N_R = 603

NI Analysis for % of Responders using Aronchick Scale at Visit 3
<table>
<tr><th>Analysis Set</th><th>Statistic</th><th>SPS+Mg n/N (%)</th><th>2L PEG-3350 and bisacodyl tablets</th><th>Treatment Difference</th><th>1-sided 97.5% CI</th></tr>
<tr><td>Intent-to-Treat</td><td>N Responders, n (%)</td><td>294
244 (83.0)</td><td>300
239 (79.7)</td><td>3.3</td><td>-2.9</td></tr>
<tr><td>Per Protocol</td><td>N Responders, n (%)</td><td>260
216 (83.1)</td><td>280
222 (79.3)</td><td>3.8</td><td>-2.8</td></tr>
</table>
Responder = Excellent, good, or fair rating; NI= noninferiority, SPS+Mg = Sodium picosulfate, magnesium oxide, and anhydrous citric acid

NI Analysis for % of Responders by Colon Segment using Ottawa Scale at Visit 3
<table>
<tr><th>Population</th><th>Area of colon</th><th>SPS+Mg n/N (%)</th><th>2L PEG-3350 and bisacodyl tablets</th><th>Treatment Difference</th><th>1-sided 97.5% CI</th></tr>
<tr><td rowspan="4">Intent-to-Treat Responders</td><td>Ascending</td><td>239/294 (81.3)</td><td>252/300 (84.0)</td><td>-2.7</td><td>-8.8</td></tr>
<tr><td>Mid</td><td>274/294 (93.2)</td><td>266/300 (88.7)</td><td>4.5</td><td>-0.1</td></tr>
<tr><td>Recto-sigmoid</td><td>271/294 (92.2)</td><td>267/300 (89.0)</td><td>3.2</td><td>-1.5</td></tr>
<tr><td>Overall: ascending, mid, and recto-sigmoid</td><td>232/294 (78.9)</td><td>234/300 (78.0)</td><td>0.9</td><td>-5.7</td></tr>
<tr><td rowspan="3">Per Protocol Responders</td><td>Ascending</td><td>211/260 (81.2)</td><td>237/280 (84.6)</td><td>-3.5</td><td>-9.8</td></tr>
<tr><td>Mid</td><td>247/260 (95.0)</td><td>249/280 (88.9)</td><td>6.1</td><td>1.5</td></tr>
<tr><td>Recto-sigmoid</td><td>243/260 (93.5)</td><td>251/280 (89.6)</td><td>3.8</td><td>-0.8</td></tr>
</table>
Responder = Excellent, good, or fair rating; NI= noninferiority, SPS+Mg = Sodium picosulfate, magnesium oxide, and anhydrous citric acid</td>
<td>
<table>
<tr><th></th><th>SPS+Mg N=269 n (%)</th><th>2L PEG-3350 and bisacodyl tablets N=302 n (%)</th></tr>
<tr><td>Any ADR</td><td>33 (11.1)</td><td>29 (9.6)</td></tr>
<tr><td>Nausea</td><td>9 (3.0)</td><td>12 (4.3)</td></tr>
<tr><td>Vomiting</td><td>4 (1.4)</td><td>6 (2.0)</td></tr>
<tr><td>Headache</td><td>8 (2.7)</td><td>5 (1.7)</td></tr>
</table>
SPS+Mg = Sodium picosulfate, magnesium oxide, and anhydrous citric acid
</td>
<td>SPS+Mg was non-inferior to 2L PEG-3350 and bisacodyl tablets in overall cleansing of the colon in preparation for colonoscopy, as measured by the Aronchick Scale. SPS+Mg was non-inferior to to 2L PEG-3350 and bisacodyl tablets in cleansing the ascending, mid, and recto-sigmoid colon in preparation for colonoscopy as measured by the Ottawa Scale. No drug-related safety concerns or novel AEs were observed.</td>
</tr>
</table>

Citation Design Analysis type Setting	**Eligibility Criteria**	**Interventions**	**Patient Population Profile**	**Efficacy Results**	**Safety Results**	**Author's conclusions (optional)** ***Critique* (optional)**
	History of colorectal surgery or upper GI surgery					The results of this study demonstrated that SPS+Mg is a safe, efficacious, and well-tolerated preparation for colonoscopy. The single-blinded design of this study allowed the patients so know which treatment they were receiving, creating the possibility of bias.

Head-to-Head Studies

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions (optional) *Critique* (optional)
Renaut (2007)[31] Comparison of Fleet® and Picoprep® for colonoscopy SB RCT Setting – The Oxford Clinic in New Zealand JADAD = 3	Inclusion criteria: requiring colonoscopy	Phospho-soda buffered saline (Fleet) group Sodium picosulphate/magnesium citrate (Picoprep) group	No specific patient population data identified.	N_R = 73 *Efficacy* Adequate: Fleet 32 (78); Picoprep 32 (93.7); P 0.06 Inadequate: Fleet 9 (22); Picoprep 2 (6.3) *Acceptable* Yes: Fleet 34 (82.9); Picoprep 32 (100); P 0.01 No: Fleet 7 (17.1); Picoprep 0 (0)	Headache Yes: Fleet 18 (43.9); Picoprep 18 (56.3) No: Fleet 23 (56.1); Picoprep 14 (43.7) Nausea Yes: Fleet 20 (48.8); Picoprep 5 (15.6); P 0.003 No: Fleet 21 (51.2); Picoprep 27 (84.4) Vomiting Yes: Fleet 3 (7.3); Picoprep 2 (6.3) No: Fleet 38 (92.7); Picoprep 30 (93.7)	*No significant difference in quality of the bowel preparation achieved, however, a significant number of patients found Picoprep more acceptable than Fleet. Also the number of patients suffering nausea was significantly less with Picoprep.*

N_R= Number randomized

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions (optional) *Critique* (optional)
Manes (2013)[20] Efficacy and acceptability of sodium picosulphate/magnesium citrate versus low-volume PEG-ascorbic acid for colon cleansing: a randomized controlled trial SB RCT Hospital setting in Italy JADAD = 3	Inclusion criteria: Adult outpatients, 18 to 85 years of age, undergoing elective colonoscopy from January to June 2011, provided informed written consent Exclusion criteria: previous colonic resection, ileus, intestinal obstruction, toxic	Picosulphate/ magnesium citrate – Take 2 satchets diluted in a glass of water 5 hours apart, starting at 5pm day before colonoscopy. Drink 3 to 4 liters of clear liquid. Split dose prescribed for procedures after 12pm (half	Pico / Mg; PEG-AA Age: 60.9; 57.8 Sex: M 76 F 64; M 85 F 60 BMI (Kg/m^2): 25.1; 25.7	N_R = 293 Adequate colon cleansing (score >2): Pico / Mg 106/140 (75.7%); PEG-AA 111/145 (76.5%) Boston Bowel Preparation Score (BBPS) score: Left 6.8; Left 6.6; Right 1.95; Right 1.96 All scores were comparable and	Pico / Mg; PEG-AA; P- No or mild discomfort: 136/140 (97.1%); 123/145 (84.8%); P< 0.0003 Willing to repeat same prep: 137/140 (97.8%); 121/145 (83.4%); P< 0.0001 Patients who received Picosulphate/magnesium citrate had significantly less bloating, belching, nausea, and vomiting, but significantly more hunger. Colonic cleansing was adequate in 89.7% of split dose regimen and 74% of	Picosulphate/ magnesium citrate and low volume PEG-ascorbic acid are both effective and safe for colonic preparation. Picosulphate/ magnesium citrate is more tolerable and palatable. For low-volume regimens, a split schedule

	megacolon, severe heart failure (NYHA Class III or IV), acute cardiovascular disease, uncontrolled arterial hypertension (systolic pressure >170 mmHg, diastolic pressure >100mmHg, severe liver cirrhosis (Child-Pugh score C) or renal failure (CrCl <30mL/min), ascites, phenylketon-uria, glucose-6-phosphate dehydro-genase deficiency, pregnancy, breast feeding	afternoon before and half morning of colonoscopy). PEG-ascorbic acid – Drink 1 liter every two hours along with 1 liter of additional clear liquid starting at 5pm on the day before colonoscopy Split dose prescribed for procedures after 12pm (half afternoon before and half morning of colonoscopy).		without significant difference.	standard regimen (p=0.041).	was associated with higher quality cleansing. Compliance of the patient is crucial to achieve effective bowel cleansing. Products associated with the best compliance, such as preparations that are low in volume and palatable, are likely to achieve the best results.

N_R= Number randomized

Citation Design Analysis type Setting	**Eligibility Criteria**	**Interventions**	**Patient Population Profile**	**Efficacy Results**	**Safety Results**	**Author's conclusions (optional)** ***Critique* (optional)**
Müller (2007)[32] Comparison of sodium picosulfate with mannitol in preparation for colonoscopy SB RCT	Inclusion criteria: Older than 18 Exclusion criteria: Possibility of intestinal sub-occlusion, emergency colonoscopy,	Mannitol group - 8 hours before the exam, patients were given 1 hour to consume 50 mL of 20% mannitol with 250 mL of orange flavored juice. Patients were	Mannitol / Sodium Picosulfate Age: 62.38 (16.19) / 60.6 (16.6) Sex: Men 23 / Women 17 / Men 21 / Women 19	N_R = 80 There were no statistically significant differences between the groups as far as colon cleanliness, acceptance, or exam duration. Mannitol / Sodium Picosulfate	There were no statistically significant differences between groups for nausea, vomiting, or abdominal pain. Mannitol / Sodium Picosulfate	The quality of colon preparation and collateral effects were similar, however, abdominal distension was more frequent in the mannitol group.

Hospital setting JADAD = 2	barium or ferrous sulphate in the past 7 days	allowed to drink additional liquid up to 3 hours before the exam. Sodium picosulfate solution - Patients received three doses of one satchel diluted in one cup of water at 8 hour intervals. Patients were allowed to drink additional liquid up to 3 hours before the exam. No antiemetic drugs were allowed.		Preparation of the colon	Interrupted	6 (15%)	2 (5%)	*While the quality between groups was similar, there was less abdominal distension in the sodium picosulfate group.*
					Poor	2 (5%)	2 (5%)	
					Intermediate	6 (15%)	5 (12%)	
					Good	11 (28%)	19 (48%)	
					Excellent	15 (38%)	12 (30%)	
				Presence of foam	Yes	10 (28%)	10 (26%)	
					No	24 (71%)	28 (74%)	
				Assessment of abdominal distension	0	22 (55%)	33 (82%)	
					1-2	4 (10%)	1 (2%)	
					3-4	1 (2%)	4 (10%)	
					5-6	1 (2%)	2 (5%)	
					7-8	8 (20%)	0 (0%)	
					9-10	4 (10%)	0 (0%)	

N_R= Number randomized

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