Sodium Sulfate, Potassium Sulfate and Magnesium Sulfate Oral Solution; PEG-3350, Sodium Chloride, Sodium Bicarbonate and Potassium Chloride for Oral Solution (SUCLEAR)

National Drug Monograph

November 2014

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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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:

- SUCLEAR is a two-component bowel cleansing product consisting of an oral sulfate solution and polyethylene glycol 3350 plus electrolyte powder for solution (PEG ES).
- In Study 1, Day-Before dosing of SUCLEAR was similar to PEG ES plus bisacodyl 10 mg in the percentage of patients with 'successful' colon cleansing (90% vs. 84%) and better than the comparator in 'excellent' bowel cleansing (48% vs. 35%; small effect size). The time to complete the bowel preparation was 1.8 hours shorter with day-before SUCLEAR than PEG ES plus bisacodyl.
- In Study 2, Split-Dose SUCLEAR was also similar to 2 L PEG ES in the percentage of patients with 'successful' colon cleansing (94% vs. 94%).
- The safety of SUCLEAR is similar to those of other PEG-based bowel cleansers with the exception that it would be advisable to avoid SUCLEAR in patients at risk for fluid and electrolyte shifts.
- The two clinical studies were designed to show noninferiority; however, the Food and Drug Administration (FDA) determined that there was insufficient data to establish noninferiority. The FDA believed that efficacy was established by showing much higher responder rates than what would be expected with placebo.

Conclusions: SUCLEAR is a combination of an oral sulfate solution and a PEG 3350 electrolyte powder for solution indicated for bowel cleansing prior to colonoscopy. The total volume of preparation plus liquids for hydration is 3.5 L and this is less than 4-L regimens of comparable PEG 3350 bowel preparations but more than the 3-L regimens of MOVIPREP and SUPREP. Based on a fair quality body of evidence, SUCLEAR is overall similar in efficacy and safety to other available PEG-E products. In the clinical trials, there were trade-offs with either Day-Before or Split-Dose regimens of SUCLEAR, with potential small benefits counterbalanced by larger volumes to be ingested, lower completion rates and higher likelihood of vomiting and overall discomfort. Further studies are needed before its role can be determined in patients at risk for fluid and electrolyte shifts. SUCLEAR is an alternative to previously approved PEG 3350-based bowel cleansing preparations. Although its drug acquisition costs are only moderately higher, there is no convincing evidence that it will be better than other PEG-E bowel preparations in avoiding costly repeat colonoscopies.

Introduction

SUCLEAR (Braintree Labs) is an osmotic cathartic comprised of two main components: (1) a sulfate salt oral solution and (2) a polyethylene glycol plus electrolyte (PEG-E) powder for solution. Each component of SUCLEAR was marketed separately by the same manufacturer (Braintree Labs) as a colon cleansing product. The sulfate salt solution component (sodium sulfate, potassium sulfate and magnesium sulfate oral solution) is equivalent to one half of the dose in SUPREP (i.e., one dose of SUCLEAR contains the equivalent of *one* 6-oz bottle of SUPREP, whereas one dose of SUPREP contains *two* 6-oz bottles). The PEG-E powder for solution component (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride) is equivalent to the formerly marketed product HALFLYTELY without the bisacodyl (10 mg). Other currently marketed products equivalent to HALFLYTELY without bisacodyl are NULYTELY (also by Braintree Labs), TRILYTE (Wallace) and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution (generic by Mylan).

HALFLYTELY was discontinued in November 2011 because of reports associating it with ischemic colitis and replaced with a tentatively approved, Novel Labs product containing a lower (5-mg) dose of bisacodyl. The exclusivity of SUPREP ended 5 August 2013 (a patent remains active until 7 March 2023). SUCLEAR was approved by the Food and Drug Administration (FDA) on 18 January 2013, before the expiration of SUPREP's exclusivity. SUPREP's exclusivity expires on 18 January 2016.

Important considerations in evaluating bowel preparations for colonoscopy include (1) the cost of the bowel preparation is relatively small compared with the cost of repeat colonoscopies (needed because of inadequate bowel evacuation in 10% to 20% of VHA patients); (2) greater adherence to completing the bowel preparation and superior bowel evacuation efficacy with a new product may actually reduce overall costs of colonoscopy despite a higher drug acquisition cost (within limits); (3) Split-Dose regimens, which recommend completion of the bowel preparation and ingestion of clear liquids for hydration up until at least 2 hours prior to the procedure, are the preferred method of administration and are the standard of care for colonoscopies. Many anesthesiologists, however, prefer the alternative Day-Before regimen, which permits at least a 6-hour period of nothing by mouth (NPO, *nil per os*) before the procedure to reduce the risk of aspiration.

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 SUCLEAR 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.

FDA Approved Indication(s)

- Cleansing of the colon as a preparation for colonoscopy in adults.

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).

- Whole bowel irrigation in poison management (e.g., enteric-coated and extended-release drugs)
- Bowel cleansing prior to barium enema X-ray examination (based on approved indications for other PEG 3350 bowel cleansers such as GOLYTELY and COLYTE WITH FLAVOR PACKS)

Current Alternatives

VA National Formulary bowel cleansers are shown in Table 1. SUCLEAR differs from the formulary line items by consisting of two components, an oral sulfate salt solution (an item not on VANF) and PEG-E powder for oral solution (on VANF).

Table 1 VA National Formulary Bowel Cleansing Agents

POLYETHYLENE GLYCOL 3350 (PEG-3350)	POWDER,ORAL
POLYETHYLENE GLYCOL 3350 (PEG-3350)/ELECTROLYTES	PWDR,RENST-ORAL
SODIUM PHOSPHATE (EQV OSMOPREP)	TAB

MOVIPREP, PEG-E with ascorbic acid powder for solution is included in the VANF line item for PEG-3350 with electrolytes. This is the only PEG-E solution on VANF that is FDA-approved for split dosing.

Alternative sodium phosphate-free bowel cleansing PEG products are shown in Table 2. SUCLEAR differs from the other products in volume and amount / concentration of electrolytes. Like SUPREP, it contains potassium sulfate and magnesium sulfate.

Table 2 Prescription Bowel Cleansing Oral Solutions

PRODUCT, TTL VOLUME INGESTED	FORM	TTL DOSE VOLUME IN WFR (L)	ADD'L LFH (L)	TOTAL DOSE (g)							OTHER
				PEG	SS	SC	SB	PC	PS	MS	
PEG 3350 ES, 4 L											
COLYTE	PFS, bottle	4 DB	Ad lib*	227.1	21.5	5.53	6.36	2.82			
GOLYTELY	PFS, packet										
PEG ES	PFS, jug	4 DB	Ad lib*	236	22.74	5.86	6.74	2.97			
GOLYTELY											
COLYTE WITH FLAVOR PACKS	PFS, bottle	4 DB	Ad lib*	240	22.72	5.84	6.72	2.98			
PEG ES											
PEG, SC, SB, PC†	PFS, bottle	4 DB	Ad lib**	420		11.2	5.72	1.48			
NULYTELY											
TRILYTE											
Combination Sulfate Salts and PEG-3350 ES, 3.5 L											
SUCLEAR (WITH FLAVOR PACKS)	Solution (Step 1)	0.5 SD 0.5 DB	1 SD 0.5 DB		17.5				3.13	1.6	Sucralose
	PFS, bottle (Step 2)	2 SD* 2 DB	Ad lib SD* 0.5 DB	210		5.6	2.86	0.74			

Cont'd

PRODUCT, TTL VOLUME INGESTED	FORM	TTL DOSE VOLUME IN WFR (L)	ADD'L LFH (L)	TOTAL DOSE (g)							OTHER
				PEG	SS	SC	SB	PC	PS	MS	
PEG-3350 ES with Ascorbic Acid, 3 L											
MOVIPREP	PFS, pouches	2 SD 2 DB	1 SD* 1 DB	200	15	5.382		2.030			SA, AA (osmotics) ACSF, ASP, PALA 131 mg
Sulfate Solution, 3 L											
SUPREP BOWEL PREP KIT	Solution	1 SD	2 SD*		17.5				3.13	1.6	Sucralose

AA, Ascorbic acid; ACSF, Acesulfame; ASP, Aspartame; DB, Day-Before regimen; ES, Electrolyte solution; MS, Magnesium Sulfate; PC, Potassium Chloride; PEG, Polyethylene glycol 3350; PFS, Powder for solution; PALA, Phenylalanine; PS, Potassium Sulfate; SA, Sodium ascorbate; SC, Sodium Chloride; SD, Split-Dose regimen; SB, Sodium Bicarbonate; SS, Sodium Sulfate; WFR, Water for reconstitution; LFH, (Clear) Liquid for hydration

*Consume up until at least 2 hours before procedure. **Consume up until at least 2 hours before procedure for NULYTELY; no guidance given for TRILYTE.

Dosage and Administration

Refer to the Prescribing Information for details.

SUCLEAR can be administered as a 2-day Split-Dose regimen (preferred method) or as a 1-day Day-Before regimen (alternative method), similar to other PEG-based bowel cleansing regimens. Any 2-L or 4-L PEG-based bowel cleansers can be administered in a split-dose manner; however, only two other products are FDA-approved for a 2-day Split-Dose regimen (MOVIPREP and SUPREP). The Day-Before regimen is the alternative method for patients in whom the split-dose method is inappropriate (e.g., early morning procedure; traveling long distance to colonoscopy; patient is to receive a barium enema).

Both SUCLEAR dosing regimens require ingestion of one 6-oz bottle of oral solution (containing sodium sulfate, potassium sulfate, and magnesium sulfate) diluted with water to 16-oz plus one (with Day-Before regimen) or two (with Split-Dose regimen) additional 16-oz containers of water, followed by the powder (polyethylene glycol 3350, sodium chloride, sodium bicarbonate and potassium chloride) dissolved in a 2-L jug of water. The instructions state that the bowel preparation must be taken in this order (oral sulfate solution first, then PEG 3350 ES solution).

The total volume ingested per dose differs between the two regimens. In the Split-Dose regimen, the amount ingested is about 1.5 L for the first dose and 2 L for the second dose. In the Day-Before regimen, the amount ingested is about 1 L for the first dose and 2.5 L for the second dose. The total amount ingested for either dosing regimen is 3.5 L, of which 2.5 L is bowel preparation and 1 L is water.

One concern with both dosing regimens is that the first doses consist only of the oral solution of sulfate salts without PEG-3350. If patients do not drink the second doses, then no PEG-3350 is ingested.

Efficacy

A literature search was performed on PubMed/Medline (1966 to July 2014) using the search terms *polyethylene glycol, PEG, sulfate, bowel cleans** and *SUCLEAR*. No search limits were applied. The search found no published articles involving SUCLEAR. Data was obtained from the FDA Division Director Summary Review, Prescribing Information, a manufacturer product flyer and a copy of an abstract submitted by McGowan J, et al.[i] to the American College of Gastroenterology (ACG) in 2013. The manufacturer did not have an Academy of Managed Care Pharmacy (AMCP) dossier.

Summary of efficacy findings

Two Phase 3 colonoscopist-blinded, multicenter (24), noninferiority (NI) randomized clinical trials (RCTs) with active comparators were performed (**Table 3**). In total, 737 adult patients were assessed for efficacy. Patients had a mean age of 57 years (range, 21 to 86 years), 46% were male and 82% were White. The clinical trials included an undisclosed number of "high risk" patients, defined as patients with reported medical history of cardiac, renal or vascular problems (hypertension) or diabetes.

Table 3 Summary of SUCLEAR Studies in Bowel Cleansing for Colonoscopy

Design, Study Population	Findings
Prescribing Information (01/2013)[ii]; FDA Summary Review[iii]; Rex, et al (2014)[iv]	
"Study 1"; Phase 3 SB MC NI RCT; 15% NI margin 366 patients undergoing elective colonoscopy Risk of Bias: R2 B1 W1 A0.	Day-Before SUCLEAR vs. Day-Before 2 L PEG ES plus 10 mg bisacodyl (PEG+BIS, equivalent to HALFLYTELY [no longer marketed]): *Similar in Terms of:* • Patients with 'successful' (4 / excellent or 3 / good) colon cleansing on the 4-point Colonoscopist Colon Cleansing scale (primary endpoint): 90% (158/176; 95% CI 84% to 94%, mITT) vs. 84% (157/188); difference, 6% (95% CI, –1% to 13%). • Cecum reached (N=172 vs. 184): 99% vs. 100% *Statistically Better in Terms of:* • Patients with 'excellent' bowel cleansing: 48% vs. 36%; diff 12% (p=0.01; small effect size) • Time to complete bowel prep: 3.7 vs. 5.5 h (diff 1.8 h; p<0.001) *Statistically Worse in Terms of:* • Patients completing entire preparation, post hoc analysis: 87% vs. 94% (p=0.033) • Overall discomfort "slightly" higher with SUCLEAR than PEG+BIS (2.06 vs. 1.76[§]; p=0.03).* No clinically relevant differences in lab results including serum electrolytes and serum creatinine.. No significant safety signals were identified. Overall safety profile resembles those for other similar colon cleansing products. *No Data Given:* • Adequacy of colon cleaning / need for re-preparation FDA determined that there was insufficient data available to establish noninferiority (e.g., lack of placebo comparisons with comparator treatment). Efficacy was established by showing that the lower bound of the confidence interval of the success rate for SUCLEAR exceeded a reasonably expected placebo response rate[†].

Design, Study Population	Findings
Prescribing Information (01/2013); FDA Summary Review[iii]; Rex, et al (2014)[iv]	
"Study 2"; Phase 3 SB MC NI RCT;15% NI margin 371 patients undergoing elective colonoscopy Risk of Bias: R2 B1 W1 A0.	Split-Dose SUCLEAR was similar to Split-Dose 2 L PEG ES (equivalent to MOVIPREP) in terms of *Similar in Terms of:* • Proportion of patients with successful (4/excellent or 3/good) colon cleansing on the 4-point Colonoscopist Colon Cleansing scale (primary endpoint): 94% (173/185; 95% CI 89% to 97%, mITT) vs. 94% (173/185); difference, 0% (95% CI, –5% to 5%). • Patients with 'excellent' bowel cleansing: 52% vs. 51% (NSD) • Cecum reached (N=181 vs. 182): 100% vs. 100% *Statistically Better in Terms of:* No outcome measures were applicable. *Statistically Worse in Terms of:* • Patients completing entire preparation: 90% vs. 98% (p=0.003) • Vomiting: 26/186 (14%) vs. 13/185 (7%); difference 7%, 95% CI –0.8 to 12.7 (p=0.042); NNT 15 (95% CI 8–150) • Bloating intensity rating was "slightly" higher with PEG ES than SUCLEAR (1.66 vs. 1.79[§]; p=0.03). No clinically relevant differences in lab results including serum electrolytes and serum creatinine. *No Data Given:* • Adequacy of colon cleaning / need for re-preparation • Time to complete bowel prep No significant safety signals were identified. Safety profile resembles those for other similar colon cleansing products. FDA determined that there was insufficient data available to establish noninferiority (e.g., lack of placebo comparisons with comparator treatment). Efficacy was established by showing that the lower bound of the confidence interval of the success rate for SUCLEAR exceeded a reasonably expected placebo response rate[†].

MC, Multicenter; NI, Noninferiority; SB, Single-blind (colonoscopist only). Abbreviations for Risk of Bias: R, Randomization, B, Blinding; W, Withdrawals; A, Allocation concealment. 1 point each if element was reported and was valid or posed low likelihood of bias. Lower number of total points reflects greater likelihood of bias.
[†] Considered to be exceedingly low and approaching 0%. [§] on scale of 1/None to 5/Severely Distressing.

Table 4 Assessment of Evidence Base

Category	Summary
Overall Quality of Studies (GRADE) (Internal validity or risk of bias)	Two noninferiority (NI) studies had insufficient data to establish noninferiority. The NI of 15% was relatively large. To determine efficacy, FDA used an alternate method used with previously approved bowel cleansing products. Potential publication bias; (Rex, et al (2014) reported that SUCLEAR was NI to both comparators, study was funded by Braintree Labs and two authors were Braintree employees.[iv] Volumes of bowel preparations differed (3.5 L vs. 2 L). Limitations: Bowel cleansing was not scored by colon segment. Adenoma counts were not done.
Consistency of Results (Within and among studies)	Mostly consistent between the two studies, although different dosage regimens and comparators were evaluated. "Successful" colon cleansing was better with SUCLEAR than the comparator with Day-Before regimen but not better with Split-Dosing.
Directness of Evidence	The primary efficacy measure was assessed directly. Need for repeating colonoscopies was not assessed directly but may be inferred by rates of 'successful' colon cleansing.
Precision of Results	The 95% CI around the success rate for SUCLEAR was relatively narrow for both studies. Descriptions for 'excellent' and 'good' scores have minor differences.

Safety

Contraindications, warnings and adverse event profiles for SUCLEAR are similar to those of other PEG-3350 plus electrolytes oral solution bowel cleansers.

Notable Adverse Events

No Reported Cases of Aspiration / Aspiration Pneumonia: Neither dosing regimen was associated with aspiration or aspiration pneumonia.[v]

Discomfort and Bloating: In general, sulfate-containing bowel preparations (COLYTE, GOLYTELY, SUCLEAR) are less palatable. In the SUCLEAR trials, discomfort and bloating were described as "slightly" but statistically higher with SUCLEAR than either PEG 2 L with bisacodyl 10 mg (day-before regimen) or PEG ES 2 L (split-dose regimen).

Laboratory Abnormalities: Relative to the comparator treatments, SUCLEAR had numerically higher rates of new-onset increased anion gap, alanine aminotransferase (ALT), creatine kinase (CK) and numerically decreased estimated creatinine clearance on the day of colonoscopy. No further follow-up laboratory tests were done.

Special Populations

Elderly

In clinical trials, data related to the use of SUCLEAR in the elderly was based on 90 patients (25% of 362) who were 65 years of age or older, and 29 patients (8%) who were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Patients at Risk of Fluid and Electrolyte Abnormalities

Sulfate is a poorly absorbed anion. In patients who did not have heart failure, renal insufficiency, end-stage liver disease, or electrolyte abnormalities, oral sulfate solution did not produce significant fluid and electrolyte abnormalities.[vi,vii] Since sulfate solution and SUCLEAR have not been tested in patients at risk for fluid shifts and electrolyte abnormalities, it would be advisable to avoid sodium sulfate-based preparations in such patients. The

Warnings and Precautions regarding serious fluid and serum chemistry abnormalities are similar for SUCLEAR and the other bowel preparation solutions, with the exception that SUCLEAR does not have the same warning about potential temporary increases in uric acid that is applicable to SUPREP.

Postmarketing Safety Experience

No information available.

Sentinel Events

None.

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:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Suclear	Suprep® Bowel Prep Kit	None	None	Sucraid Sucralfate

Drug Interactions

Drug-Drug Interactions

The drug-drug interactions with SUCLEAR are similar to those for other PEG 3350 ES products.

- Drugs that increase risks due to fluid and electrolyte changes
- Oral medication taken within 1 hour of each dose may not be absorbed properly
- Concurrent use of stimulant laxatives may increase the risk of ischemic colitis

Pharmacoeconomic Analysis

None.

Conclusions

SUCLEAR is a combination of an oral sulfate solution and a PEG 3350 electrolyte powder for solution indicated for bowel cleansing prior to colonoscopy. The total volume of preparation plus liquids for hydration is 3.5 L and this is less than 4-L regimens of comparable PEG 3350 bowel preparations but more than the 3-L regimens of MOVIPREP and SUPREP. Based on a fair quality body of evidence, SUCLEAR is overall similar in efficacy and safety to other available PEG-E products. In the clinical trials, there were trade-offs with either Day-Before or Split-Dose regimens of SUCLEAR, with potential small benefits counterbalanced by larger volumes to be ingested, lower completion rates and higher likelihood of vomiting and overall discomfort. Further studies are needed before its role can be determined in patients at risk for fluid and electrolyte shifts. SUCLEAR is an alternative to previously approved PEG 3350-based bowel cleansing preparations. Although its drug acquisition costs are only moderately higher, there is no convincing evidence that it will be better than other PEG-E bowel preparations in avoiding costly repeat colonoscopies.

Prepared November 2014. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager

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