

Sucroferric Oxyhydroxide (VELPHORO®) National Drug Monograph September 2014

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

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Executive Summary

Indication

- Sucroferric oxyhydroxide (VELPHORO) is an iron-based phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis.

Efficacy

- Treatment with sucroferric oxyhydroxide (1.0 to 3.0 gm per day) was found to be non-inferior to sevelamer carbonate (4.8 to 14.4 gm per day) in reducing serum phosphorus at 12 weeks in 1,055 patients with CKD on dialysis.
- The mean number of tablets per day for the first 12 weeks was 2.8 sucroferric oxyhydroxide and 7.6 sevelamer carbonate; when including data up to week 24, the mean number of tablets was 3.1 and 8.1, respectively.
- In the same study in patients with controlled serum phosphorus (< 5.5 mg/dl) at 24 weeks, maintenance dose sucroferric oxyhydroxide was superior to low dose (250 mg; found to be ineffective per a dose-response study) sucroferric oxyhydroxide at 27 weeks.

Safety

- More patients treated with sucroferric oxyhydroxide (83.2%) reported at least one treatment-emergent adverse event (TEAE) compared to sevelamer carbonate (76.1%).
- Withdrawals due to TEAEs were reported in 15.7% of patients treated with sucroferric oxyhydroxide compared to 6.6% treated with sevelamer carbonate.
- The most common TEAE reported with sucroferric oxyhydroxide (and more frequent than sevelamer carbonate) included diarrhea, discolored feces, and hyperphosphatemia.

Conclusions

- Treatment with sucroferric oxyhydroxide, an iron-based phosphate binder, was shown to be safe and effective in reducing serum phosphorus in patients with CKD on dialysis, and was non-inferior to the non-aluminum, non-calcium phosphate binder, sevelamer carbonate.
- More patients treated with sucroferric oxyhydroxide reported adverse events, or withdrew due to an adverse event, compared to sevelamer carbonate. There are no published data on the safety or long-term outcomes of sucroferric oxyhydroxide compared to other phosphate binders.
- There is the potential for decreased pill burden with sucroferric oxyhydroxide compared to sevelamer carbonate tablets; although, the number of daily doses with sucroferric oxyhydroxide appear to be similar to prescribing recommendations for lanthanum carbonate or sevelamer carbonate powder.

Place in Therapy

Sucroferric oxyhydroxide may be considered in patients with CKD on dialysis who meet criteria for a VA National Formulary non-calcium, non-aluminum phosphate binder (i.e., lanthanum carbonate, sevelamer carbonate; refer to VA criteria for use) and 1) documented intolerance to a trial of both lanthanum carbonate and sevelamer carbonate; or 2) difficulty with adherence due to pill burden with sevelamer carbonate and after a trial of lanthanum carbonate; or 3) difficulty with swallowing sevelamer carbonate tablets and after a trial of chewable lanthanum carbonate tablets, and then non-formulary sevelamer carbonate powder; or 4) patient is pregnant and risk vs. benefit has been considered and it has been determined that the patient will continue on a non-calcium, non-aluminum phosphate binder or the patient is of child-bearing potential and it has been determined that the patient will continue on a non-calcium, non-aluminum phosphate binder if the patient becomes pregnant.

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Introduction^{1,2}

Sucroferric oxyhydroxide is the first iron-based phosphate binder approved for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.¹ Other available non-aluminum, non-calcium based phosphate binders include lanthanum carbonate and sevelamer carbonate or hydrochloride.

In patients with CKD on dialysis, treatment guidelines suggest lowering serum phosphorus levels toward the normal range,² with implementation of a phosphate restricted diet as well as treatment with phosphate binders often required as part of therapy in these patients.² Non-aluminum, non-calcium phosphate binders were developed to offer an alternative to aluminum or calcium-based phosphate binders that may be limited by side effects including aluminum toxicity or hypercalcemia (with the potential for increased risk for vascular calcifications), respectively.² With conflicting data, further research is needed to determine whether there is a difference in long-term clinical outcomes with calcium-based vs. non-aluminum, non-calcium based phosphate binders in patients with CKD.² The non-aluminum, non-calcium based phosphate binders, lanthanum carbonate and sevelamer carbonate, are available on the VA National Formulary and are reserved for patients with CKD and hyperphosphatemia according to national VA criteria for use.

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 sucroferric oxyhydroxide 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.

Clinical Pharmacology^{1,3}

Sucroferric oxyhydroxide includes the active moiety polynuclear iron(III)-oxyhydroxide, which is not absorbed. Binding of dietary phosphate occurs by ligand exchange in the gastrointestinal tract, with the bound phosphate eliminated in the feces.¹

Although polynuclear iron(III)-oxyhydroxide is not absorbed, its degradation product can be released and absorbed. The median iron uptake from 2 gm elemental iron per day (10 gm per day sucroferric oxyhydroxide) for 1 week was reported to be 0.06% for non-dialysis CKD patients, 0.02% for patients on hemodialysis, and 0.43% in healthy volunteers.^{1,3}

FDA Approved Indication¹

Sucroferric oxyhydroxide (VELPHORO) is an iron-based phosphate binder indicated for the control of serum phosphorus levels in patients with CKD on dialysis.¹

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Potential Off-Label Uses^{1,3}

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](#) (VA PBM Intranet site only).

Sucroferric oxyhydroxide has not been studied in patients with CKD not on dialysis, or in patients with CKD specifically requiring iron supplementation, to determine the efficacy, safety, or appropriate use in these patient populations.^{1,3}

Current VA National Formulary Alternatives^{1,2}

The tablet formulations of the non-aluminum, non-calcium phosphate binders, lanthanum carbonate and sevelamer carbonate are available on the VA National Formulary, restricted to national VA criteria for use. The powder formulation of sevelamer carbonate is available nonformulary.

Calcium carbonate and calcium acetate are calcium-based phosphate binders available on the VA National Formulary.

Non-Aluminum, Non-Calcium Phosphate Binder	FDA Approved Population
<i>VANF</i>	
Lanthanum carbonate tablet	ESRD
Sevelamer carbonate tablet	CKD on dialysis
<i>Nonformulary</i>	
Sevelamer carbonate powder	CKD on dialysis
Sevelamer hydrochloride ^a	CKD on dialysis

CKD=chronic kidney disease; ESRD=end stage renal disease; FDA=Food and Drug Administration; VANF=VA National Formulary
^a Sevelamer hydrochloride is available nonformulary; transition from sevelamer hydrochloride to sevelamer carbonate per manufacturer announcement January 2009

Dosage and Administration¹

Each tablet of sucroferric oxyhydroxide contains 500 mg iron (2,500 mg sucroferric oxyhydroxide). The initial recommended dose is one 500 mg tablet three times daily with meals, or 1,500 mg per day. The dose can be titrated as needed to achieve the desired serum phosphorus level, with recommendations to adjust the dose by one tablet per day, which may be titrated as often as on a weekly basis. The maximum recommended dose is 3,000 mg daily (total of 6 tablets per day). Sucroferric oxyhydroxide must be chewed (or crushed), and not swallowed whole.¹

Efficacy^{4,5}

A literature search was performed on PubMed/Medline using the search term sucroferric oxyhydroxide or PA21 through 21 Jul 2014. Reference lists of review articles were searched for additional relevant information.

Efficacy Measures⁴

Primary Endpoint

- Change in serum phosphorus (week 24 vs. 27): superiority of maintenance dose vs. low dose sucroferric oxyhydroxide

Secondary Endpoint

- Change in serum phosphorus (baseline to week 12): non-inferiority of sucroferric oxyhydroxide vs. sevelamer carbonate

Clinical Trial Data^{1,4,5}

The efficacy and safety of sucroferric oxyhydroxide was evaluated in a multicenter, randomized, open-label, active-controlled trial in patients with CKD on dialysis (approximately 92% hemodialysis). Patients with serum phosphorus ≥ 1.94 mmol/l (i.e., ≥ 6.0 mg/dl) after a 2 to 4 week wash-out period received initial treatment with sucroferric oxyhydroxide 500 mg tablet twice daily (1.0 gm/day) or sevelamer carbonate 800 mg two tablets three times daily (4.8 gm/day), with doses to be taken with meals. Doses were titrated based on efficacy or tolerability over 8 weeks, followed by a 4 week period where dose adjustment was only allowed for tolerability. The dose was continued for an additional maintenance period of 12 weeks where the dose could be adjusted based on efficacy or tolerability. The dose range allowed for sucroferric oxyhydroxide was 1.0 gm to 3.0 gm daily, and for sevelamer carbonate, 2.4 gm to 14.4 gm daily. Concomitant medications including vitamin D, vitamin D analogs, calcimimetics were to remain unchanged (as far as possible, per methods).⁴

The mean age of participants was 56 years, with approximately 58% male, and 77% Caucasian. Patients received previous phosphate-binder therapy as follows: calcium-based (65.3%); sevelamer (34.8%), lanthanum (5.7%). Patients were excluded if they had an intact parathyroid hormone (iPTH) level > 800 ng/ml (> 88 pmol/l) or pending parathyroidectomy, significant gastrointestinal (GI) or hepatic disorders or major GI surgery, or serum ferritin > 4494 pmol/l (> 2000 mcg/l). Patients receiving peritoneal dialysis with either a history of peritonitis in the past 3 months or ≥ 3 episodes in the previous 12 months were excluded. Patients with hypercalcemia on non-calcium phosphate binders, or those with hypocalcemia, were also excluded. Treatment withdrawals occurred in 27.5% (195 of 710) patients receiving sucroferric oxyhydroxide compared to 16.0% (56 of 349) randomized to sevelamer carbonate. Twelve patients (6.2%) withdrew from treatment with sucroferric oxyhydroxide for hyperphosphatemia; none were withdrawn for this reason in the sevelamer carbonate treatment group.

As per the table below, the primary endpoint of mean change in serum phosphorus (week 24 to 27) was significantly higher in patients treated with 250 mg sucroferric oxyhydroxide (dose found to be ineffective based on a dose-response study)⁵ compared to the patients continued on maintenance dose sucroferric oxyhydroxide.⁴

Primary Endpoint⁴

Sucroferric oxyhydroxide	n	Mean Phosphorus (mmol/l)		
		Week 24	Δ at Week 27	P value
Maintenance Dose ^a	50	1.5	NS ^b	< 0.001
Low Dose	49	1.6	0.6	

Conversion phosphorus mg/dl x 0.3229 = mmol/l

^a Mean dose for 50 of the 99 patients re-randomized to maintenance or low dose not provided; the mean number of tablets was 3.6 (1.8 gm/day) from week 12 to 24 for cohort of 694 patients on sucroferric oxyhydroxide

^b Phosphorus level not provided; reported as no significant change from week 24 to 27

The secondary endpoint of mean change in serum phosphorus from baseline to week 12 was reported to be non-inferior between treatment with sucroferric oxyhydroxide and sevelamer carbonate (refer to Table below).⁴

Secondary Endpoint⁴

Treatment	n ^a	Mean Phosphorus (mmol/l)		
		Baseline	Δ at Week 12	Difference
Sucroferric oxyhydroxide	685	2.5	-0.71	0.08 ^b
Sevelamer carbonate		2.4	-0.79	

^a Results shown for per-protocol set (PPS)

^b Noninferior based on upper bound 97.5% confidence interval of least-squares mean difference in change from baseline to week 12 of 0.15 mmol/l, less than pre-defined margin of 0.19 mmol/l

There was a significant decrease from baseline to week 24 in median serum iPTH in both treatment groups, with a larger decrease in the sucroferric oxyhydroxide treatment group compared to sevelamer carbonate (-4.49 vs. -1.59 pmol/l, respectively; P=0.04). Median serum 25(OH)D decreased significantly in both groups, with a greater decrease with sevelamer carbonate (P=0.019). There was a significant decrease in median 1,25(OH)₂D with sevelamer carbonate (P=0.0316 for difference compared to sucroferric oxyhydroxide). Median serum ferritin increased in both treatment groups, with an increase in transferrin saturation with sucroferric oxyhydroxide (P<0.0001) vs. sevelamer carbonate. Serum iron was increased with sucroferric oxyhydroxide compared to sevelamer carbonate (P=0.0296). There was no significant difference in change in hemoglobin between treatment groups. The authors noted that the majority of patients were also receiving intravenous iron therapy.⁴

The mean number of tablets per day for the first 12 weeks was 2.8 for sucroferric oxyhydroxide and 7.6 for sevelamer carbonate; when including data up to week 24, the mean number of tablets was 3.1 and 8.1, respectively.⁴ It is noted that the starting dose in the clinical trial of 500 mg twice daily (2 tablets daily) differs from the product information recommending a starting dose of sucroferric oxyhydroxide 500 mg three times daily (3 tablets daily), with maximum 3.0 gm daily (6 tablets daily).¹ Adherence (based on number of tablets returned by patients) from baseline to week 24 was reported as 82.6% with sucroferric oxyhydroxide and 77.2% with sevelamer carbonate.⁴

Safety Data^{1,4,5}

Deaths and Other Serious Adverse Events^{1,4,5}

In one Phase III clinical trial, nine deaths were reported as the reason for treatment withdrawal in patients treated with sucroferric oxyhydroxide, and in five patients in the sevelamer carbonate treatment group. Deaths were reported in 1.8% of 707 and 2.0% of 348 patients in the sucroferric oxyhydroxide and sevelamer carbonate treatment groups, respectively. The authors reported that no fatal treatment-emergent adverse events (TEAEs) were related to study drug and that the deaths were mostly related to

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cardiac disorders (no additional information provided).⁴ In a dose finding study, one patient treated with sucroferric oxyhydroxide (reported dose of 5.0 gm per day, equivalent to 1 gm iron daily), died due to a gastrointestinal hemorrhage and cardiac arrest that were not related to the study drug per the investigator.⁵

Severe adverse events considered to be related to study drug were reported in 1.0% of patients treated with sucroferric oxyhydroxide and 1.1% of patients in the sevelamer carbonate treatment groups; serious adverse events related to study drug were reported in 0.3% and 0% of patients in the sucroferric oxyhydroxide and sevelamer carbonate treatment groups, respectively.⁴

Common Adverse Events^{1,4}

According to the product information, adverse reactions occurring in > 5% of patients treated with sucroferric oxyhydroxide include diarrhea, discolored feces, and nausea.¹ The most common adverse reactions resulting in treatment withdrawal include diarrhea (4%), abnormal product taste (2%), and nausea (2%).¹ A comparison of overall TEAE and TEAE occurring in ≥ 5% of patients in a Phase III clinical trial is listed in the table below.⁴

Adverse Event	Sucroferric oxyhydroxide n=707 (%)	Sevelamer carbonate n=348 (%)
Any TEAE	83.2	76.1
Any GI TEAE	45.1	33.6
Diarrhea	20.1	7.5
Discolored feces	15.4	0.3
Hyperphosphatemia	11.2	7.8
Nausea	7.2	11.2
Hypertension	6.4	7.5
Vomiting	4.4	5.5
Constipation	3.8	7.2

GI=gastrointestinal; TEAE=treatment-emergent adverse event

Sentinel Events

No data.

Contraindications¹

None.

Warnings and Precautions¹

Monitoring in Patients with Gastrointestinal Disorders or Iron Accumulation Disorders

Patients with the following conditions have not been included in clinical trials with sucroferric oxyhydroxide: peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major GI surgery, or history of hemochromatosis or other disease with iron accumulation; therefore, the manufacturer recommends to monitor for effect and iron homeostasis in these patients receiving treatment with sucroferric oxyhydroxide.¹

Special Populations¹

Pregnancy

Ferric carboxymaltose is Pregnancy Category B. Sucroferric oxyhydroxide has not been adequately studied in pregnant women. Treatment with sucroferric oxyhydroxide should only be used during pregnancy if clearly indicated.¹

Nursing Mothers

The manufacturer states that due to the minimal absorption of sucroferric oxyhydroxide, excretion of the drug in breast milk is unlikely.¹

Demographics (Age)

Approximately 30% of patients in two clinical trials of sucroferric oxyhydroxide were 65 years of age or older, with no reported differences in safety or effectiveness in older compared to younger patients.¹

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

As part of a Joint Commission standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA 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
Sucroferric oxyhydroxide 500 mg chewable tablet	Iron sucrose Sucrose	None	None	Serophene Sarafem Sucralfate Sodium ferric gluconate
VELPHORO	None	None	None	Venofer Vfend

Drug Interactions¹

Based on in vitro data, sucroferric oxyhydroxide should not be administered in patients taking oral formulations of levothyroxine or vitamin D analogs. If alendronate or doxycycline is prescribed in patients taking sucroferric oxyhydroxide, they should be administered 1 hour prior to taking sucroferric oxyhydroxide.¹

Acquisition Prices

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis⁶

No published pharmacoeconomic analyses comparing sucroferric oxyhydroxide with other available phosphate binders are available.

One analysis of pill burden in a cohort of patients with CKD on dialysis reported the overall median number of 9 phosphate binder pills taken daily: sevelamer monotherapy, 9; calcium monotherapy, 9; lanthanum monotherapy, 6; combination therapy, 13. Median adherence was reported as 72%. There was a significant inverse association between pill burden and adherence to phosphate-binders; however the trend was nonlinear, where a decrease in adherence was noted only when the phosphate binder pill burden was more than 12 per day.⁶ Per the respective product information, the recommended starting dose of sevelamer carbonate is 800 mg to 1600 mg (1 to 2 tablets) three times daily (i.e., 3 to 6 tablets daily), with mean doses of approximately 7.2 gm daily (equivalent to nine 800 mg tablets or three 2.4 gm packets daily);⁷ patients required 1,500 to 3,000 mg daily lanthanum carbonate (equivalent to three 500 mg or 1.0 gm tablets);⁸ and on average patients required 3 to 4 tablets sucroferric oxyhydroxide per day to control serum phosphorus.¹

Conclusions

Treatment with sucroferric oxyhydroxide, an iron-based phosphate-binder, was shown to be safe and effective in reducing serum phosphorus in patients with CKD on dialysis, and was non-inferior to the non-aluminum, non-calcium based phosphate binder, sevelamer carbonate. The clinical impact of potential iron absorption with sucroferric oxyhydroxide was not able to be determined based on the data. More patients treated with sucroferric oxyhydroxide reported adverse events, or withdrew due to an adverse event, compared to sevelamer carbonate. The most common adverse events reported with sucroferric oxyhydroxide included diarrhea, discolored feces, and hyperphosphatemia. There are no published data on the safety or long-term outcomes of sucroferric oxyhydroxide compared to other phosphate binders. There is the potential for decreased pill burden with sucroferric oxyhydroxide compared to sevelamer carbonate tablets; although, the number of daily doses appear to be similar to prescribing recommendations for lanthanum carbonate or sevelamer carbonate powder.

Place in Therapy

Sucroferric oxyhydroxide may be considered in patients with CKD on dialysis who meet criteria for a VA National Formulary non-calcium, non-aluminum phosphate binder (i.e., lanthanum carbonate, sevelamer carbonate; refer to criteria for use available at [VA Criteria for Use](#)) and 1) documented intolerance to a trial of both lanthanum carbonate and sevelamer carbonate; or 2) difficulty with adherence due to pill burden with sevelamer carbonate and after a trial of lanthanum carbonate; or 3) difficulty with swallowing sevelamer carbonate tablets and after a trial of chewable lanthanum carbonate tablets, and then non-formulary sevelamer carbonate powder; or 4) patient is pregnant and risk vs. benefit has been considered and it has been determined that the patient will continue on a non-calcium, non-aluminum

phosphate binder or the patient is of child-bearing potential and it has been determined that the patient will continue on a non-calcium, non-aluminum phosphate binder if the patient becomes pregnant.

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