

Month/Year of Review: May 2014

PDL Classes: Phosphate Binders

New Drug Evaluation: Sucroferric Oxyhydroxide (Velphoro®)

Date of Last Review: September 2012

Source Document: Provider Synergies

Dossier Received: Yes

Current Status of PDL Class:

- Preferred Agents: CALCIUM ACETATE
- Non-preferred Agents: SEVELAMER (RENAGEL®), SEVELAMER CARBONATE (REVELA®), LANTHANUM CARBONATE (FOSRENOL®), CALCIUM CARBONATE/MAG CARB (MAGNEBIND®)

Previous Conclusions & Recommendations:

1. Pediatric safety and efficacy not yet determined.
2. Calcium based binders (based on evidence) especially in infants and younger children may be OK.
3. Sevelamer and calcium based (opinion based) may be ok in older children and adolescents.
4. Lanthanum long-term effect on bone is unclear.
5. Consider step therapy with calcium acetate first then resin based agents.

Background:

Since the previous review of phosphate binders, a new drug with a novel mechanism of action, sucroferric oxyhydroxide has been approved. It has been studied in a phase 2 dose-finding trial, an open-label phase 3 trial comparing it to sevelamer, and a long-term extension study that is unpublished at this time. The phase 3 study showed is non-inferior to sevelamer at reducing serum phosphorus after 12 weeks of treatment. While pill-burden was lower in patients treated with sucroferric oxyhydroxide, patients in either treatment group had adherence rates >70%, the predefined threshold for adherence. The most common adverse reactions were gastrointestinal and mild to moderate in nature.

This updated review also includes data from a meta-analysis published in 2013. This trial compared calcium-based phosphate binders to non-calcium-based phosphate binders. The authors found a 22% reduction in mortality among patients who used non-calcium-based phosphate binders compared to those using calcium-based phosphate binders. Serum phosphate levels were similar across both groups, so it is unclear how treatment with non-calcium-based phosphate binders leads to improved mortality. Mortality benefits were not observed when the non-calcium phosphate binders were evaluated individually. These results align with an open-label Italian trial, which found that sevelamer had a lower incidence of cardiovascular mortality compared to calcium carbonate, although there were many limitations to this trial and results should be interpreted with caution.

The Kidney Disease International: Global Outcomes Clinical Practice Guidelines (KDIGO) recommendations pertaining to phosphate binders have not been updated at this time. The KDIGO guidelines indicate that the choice of phosphate binder should take into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile.

Conclusions and Recommendation:

1. Phosphate binders should be selected based on each patient's specific clinical needs.
2. Consider adding a non-calcium-based phosphate binder to the preferred class, based on cost. There is no evidence that shows that one agent is more effective or safer than an alternative, however there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide.
3. Evaluate comparative costs in executive session.

PA Criteria/QL: Default prior authorization required for non-preferred drugs to ensure that non-preferred drugs are used for an above-the-line condition

Methods:

A MEDLINE OVID search was conducted using all included drugs and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2012 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. A search for any new evidence demonstrating a benefit in adult indications was also done. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews (no updates since previous review):

Cochrane Collaboration

A systematic review from the Cochrane Collaboration assessed the benefits and harms of phosphate binders in adults with chronic kidney disease (CKD).¹ From a literature search through March 2010, 60 studies (7631 participants) were identified, comparing phosphate binders to placebo or other phosphate binders. There were two independent reviewers who assessed the risk of bias for the included studies, and concluded overall that the study quality varied among the included studies. The following contributed to the overall quality variance: allocation concealment was adequate in approximately 18% of the studies and unclear in others; participants and investigators were blinded in approximately 17% of the studies and outcome assessors were blinded in none of the studies; 22% were analyzed on an intention-to-treat basis; and lost-to-follow-up ranged from 0-31%, but did not differ between the treatment and control groups of the studies. Overall, there was no significant reduction in all-cause mortality (10 studies, 3,079 participants: RR 0.73, 95% CI 0.46 to 1.16) or serum calcium-phosphorus (Ca x P) product with sevelamer hydrochloride compared to calcium-based agents.¹ The Ca x P product has been shown with limited evidence to increase the risk for development of calcification and possibly increase the risk for lower patient survival in CKD if it is >55 mg²/dL².² There was a significant reduction in serum phosphorus (16 studies, 3126 participants: MD 0.23 mg/dL, 95% CI 0.04 to 0.42) and parathyroid hormone (PTH) (12 studies, 2551 participants; MD 56 pg/mL, 95% CI 26 to 84), but a significant increase in the risk of hypercalcemia (12 studies, 1144 participants: RR 0.45, 95% CI 0.35 to 0.59) with calcium-based agents compared to sevelamer hydrochloride.¹ There was a significant increase in the risk of adverse gastrointestinal events with sevelamer hydrochloride in comparison to calcium salts (5 studies, 498 participants: RR 1.58, 95% CI 1.11 to 2.25). Compared with calcium-based agents, lanthanum significantly reduced serum calcium (2 studies, 122 participants: MD -0.30 mg/dL, 95% CI -0.64 to -0.25) and the Ca x P product, but not serum phosphorus levels. There was no significant difference in phosphorus levels with calcium acetate in comparison to calcium carbonate (5 studies, 143 participants, MD -0.19

mg/dL, 95% CI -0.61 to 0.24).¹ Authors concluded that all phosphate binders reduce serum phosphorous when compared to placebo, and there is insufficient data to conclude the comparative superiority of novel non-calcium agents over calcium-containing binders for patient centered outcomes of all-cause mortality and cardiovascular end-points in CKD.¹ The primary advantage of more recently developed phosphate binders (lanthanum carbonate and sevelamer hydrochloride) is a reduction in hypercalcemia.

Another Cochrane review from 2010 investigated the benefits and harms of interventions for the prevention and treatment of bone disease in children with CKD.³ A total of 15 randomized controlled trials (369 children) were identified, but only four studies included phosphate binders as the intervention. Overall, the quality of the evidence was very low for both the comparison of calcium carbonate versus sevelamer and calcium carbonate versus aluminum hydroxide in all measured outcomes because of small patient numbers, large loss to follow-up and risk of bias in study design.³ The authors concluded that phosphate binders (aluminum hydroxide, calcium carbonate or acetate and sevelamer) had indistinguishable effects in lowering serum phosphate, reducing PTH and on mean height standard deviation score (SDS) but that hypercalcemia was more common with calcium-containing binders.³

Meta-Analyses:

A meta-analysis published in 2013 reviewed the effects of calcium-based versus non-calcium based phosphate binders on mortality and included a total of 18 trials (11 randomized trials) with 3,409 patients receiving non-calcium-based phosphate binders (sevelamer or lanthanum) and 4,026 receiving calcium-based phosphate binders (calcium carbonate or calcium acetate).⁴ Trials ranged in size from 42 to 2,103 with median duration of follow up between 5 and 44 months. Five of the studies were rated as having a high risk of bias, due to large losses of follow-up, shortage of documentation in key tool domains, inadequate sequence generation, allocation concealment and/or blinding. The analysis of the 11 randomized trials (4622 patients with 939 deaths) found a reduction in all-cause mortality of 22% in the non-calcium-based binders compared with those who received the calcium-based phosphate binders (risk ratio 0.78, 95% CI 0.61-0.98). The mortality difference was only noted in the five trials that reported outcomes at 24 months. The mortality decrease was not statistically significant when the two non-calcium-based phosphate binders were looked at individually. The relative risk of mortality for sevelamer was 0.89 (95% CI 0.78-1.01) and 0.74 (95% CI 0.49-1.13) for lanthanum when compared to those randomly assigned to calcium-based phosphate binders. The mortality difference was not linked to phosphate reduction, due to the near equal phosphate levels in the two groups. While the authors hypothesized that the mortality difference may be due to the slowing of vascular calcification in the non-calcium-based phosphate binders, this has not been shown in clinical trials. Only two trials reported information on cardiovascular events, showing a RR of 0.85 (95% CI 0.35-2.03) for the non-calcium based phosphate binder sevelamer (lanthanum not studied). The meta-analysis was not able to find mortality difference between the 2 different non-calcium-based binders, sevelamer and lanthanum.

A previously-reviewed meta-analysis compared sevelamer and calcium-based phosphate binders (CBPB) on cardiovascular calcification in hemodialysis (HD) patients.⁵ It included 14 trials with a total of 3,271 patients.⁵ The duration of the trials ranged from 8 weeks to 45 months. The Jadad score was used to assess the quality of the trials, and six out of 14 trials ended up scoring three or more on the score, which is considered a high quality trial.⁶ All 14 trials included statements regarding randomization and five of the trials described the detailed methods used for randomization. Four trials reported changes in the coronary artery calcium (CAC) score from baseline, but taken together, there was no significant difference between the sevelamer group and the CBPB group (weighted mean difference -74.87; 95% CI -159.96 to 10.22). The levels of intact parathyroid hormone were significantly higher in the sevelamer groups than in the CBPB group (weighted mean difference 55.85; 95% CI 14.47-97.24). Overall, the authors concluded that the meta-analysis found no significant differences in cardiovascular calcification between sevelamer and CBPB. Sevelamer-treated patients had higher intact parathyroid hormone levels, lower phosphorus levels, lower calcium-phosphorus product, and fewer episodes of hypercalcemia without altering serum calcium.⁵

Guidelines (no updates since previous review):

Kidney Disease International: Global Outcomes Clinical Practice Guidelines (KDIGO)⁷

The most recent guideline published that discusses the use of phosphate binders in CKD is the KIDGO Clinical Practice Guidelines from 2009. The AGREE II guideline appraisal tool was used to assess the overall quality of the KDIGO guidelines.⁸ The overall quality of the guidelines was considered six out of seven for highest possible quality, and would be recommended for use. Areas for improvement included the search method (only the Medline search database was used), the evidence and recommendation connection (some of the recommendations were opinions only due to lack of randomized controlled trials), and there was minimal discussion on the influence of the funding body.

The KDIGO guidelines graded the strength of their recommendations by providing levels (level 1=strong evidence; level 2=weak evidence) and grades (A=high quality; B=moderate; C=low; D=very low) for the quality of evidence used to back up their recommendations. The following are the major recommendations:

- For patients with CKD stages 3-5, maintaining serum phosphorous in the normal range is suggested (2.5-4.5 mg/dL) (level of evidence 2C).
- In patients with CKD stage 5D, lowering elevated phosphorus levels toward the normal range is suggested (2C).
- In patients with CKD stages 3-5 (2D) and 5D (2B), using phosphate-binding agents in the treatment of hyperphosphatemia is suggested. The choice of phosphate binder should take into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile (not graded).
- In patients with CKD stages 3-5D and hyperphosphatemia, it is recommended to restrict the dose of calcium-based phosphate binders in the presence of persistent or recurrent hypercalcemia (1B).
- In patients with CKD stages 3-5D and hyperphosphatemia, restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low is suggested (2C).
- In patients with CKD stages 3-5D, avoiding long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication is recommended (1C).
- In patients with CKD stages 3-5D, limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments is suggested (2D).
- In patients with CKD stages 5D, increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia is recommended (2C).

NEW DRUG: SUCROFERRIC OXYHYDROXIDE (VELPHORO)

Background:

Sucroferric oxyhydroxide was approved in November 2013 for controlling phosphorus levels in patients with chronic kidney disease on dialysis. It's an iron-based phosphate binder and is available as a flavored, chewable tablet that can be taken without water.

INDICATION	DOSAGE FORM	DOSE	MECHANISM OF ACTION
Control of serum phosphorus levels in patients with chronic kidney disease on dialysis	500mg chewable tablets	1,500mg daily (divided with 3 meals). Adjust by 1 tablet per day as needed until an acceptable serum phosphorus level (<= 5.5 mg/dL). Titrate	Ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and the phosphate in the dilate. The bound phosphate is eliminated with feces. Serum phosphorus

		as often as weekly.	and calcium-phosphorus levels are reduced.
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Efficacy:

The efficacy and safety of sucroferric oxyhydroxide was evaluated in three clinical trials: a phase 2 dose-finding study, a phase 3 randomized trial, and a long-term extension study.

The Phase 2 dose-ranging study was a parallel-group, randomized, open-label, active-controlled, trial, comparing five dosage regimens of sucroferric oxyhydroxide. Subjects (n=150) were receiving dialysis three times per week for ≥3 months and had a serum phosphorus >5.5mg/dL. Subjects were randomized to receive one of the following regimens: 1.25, 5, 7.5, 10, or 12.5 g/day. Those randomized to the control group received 4.8 g/day of sevelamer. After 6 weeks of treatment, a dose dependent response was observed, with the highest responses observed in patients receiving 10 or 12.5 g/day. The 5 and 7.5mg doses resulted in a response similar to that of sevelamer, but the study was not designed to directly compare the different treatment options. Adverse events were considered mild to moderate and not dose dependent, with a 10.9% discontinuing treatment due to adverse events.^{9,10}

A Phase 3, open-label, active controlled trial, compared sucroferric oxyhydroxide to sevelamer in patients with chronic kidney disease, undergoing dialysis. Of the 1,059 subjects included in the trial, 1,041 were included in the full analysis set, as they had received at least one dose of study medication and had at least one post baseline evaluable efficacy assessment. Patients were treated for 24 weeks total (8 weeks of dose titration, 4 weeks with no dose change, 12 weeks maintenance). After 24 weeks, patients were randomized to a maintenance dose (MD) or a low-dose (LD) control of 250 mg/day of sucroferric oxyhydroxide and assessed at week 27. The primary efficacy endpoint was the superiority of MD compared to LD. Change in serum phosphorus after 12 weeks of treatment was evaluated as a secondary endpoint. Adherence was measured, but a formal comparison was not conducted.^{9,11}

After 12 weeks of treatment, sucroferric oxyhydroxide was non-inferior to sevelamer for change in serum phosphorus levels (-0.71 mmol/L vs -0.79 mmol/L, respectively). After 24 weeks, mean serum phosphorus concentrations were similar for patients receiving MD and LD sucroferric oxyhydroxide, 1.5 mmol/l and 1.6 mmol/l, respectively. Patients treated with LD sucroferric oxyhydroxide experienced a significantly larger increase in serum phosphorous levels after 3 weeks (p<0.001). More patients experienced at least one treatment emergent adverse event (TEAE) in the sucroferric oxyhydroxide -treated group, versus those in the sevelamer-treated group (83.2% vs 76.1%). The most commonly reported adverse events were diarrhea, discolored stools, and hyperphosphatemia. Severe TEAE's were infrequent and similar between the two groups (1% vs 1.1%). There was a higher incidence of TEAEs leading to withdrawal in the sucroferric oxyhydroxide group (15.7%) versus the sevelamer group (6.6%). On average, patients in the sucroferric oxyhydroxide group took 3.1 tablets per day, compared to 8.1 in the sevelamer group, and both groups were considered to be adherent (82.6% in the sucroferric oxyhydroxide group vs 77.2% in the sevelamer group), as indicated by the pre-specified threshold of 70%.^{9,11}

Aside from the limitation of the open-label trial design, the starting sucroferric oxyhydroxide treatment regimen consisted of twice daily dosing. Patients receiving this treatment were initially experiencing at least one meal without a phosphate binder until the dose was increased to three times daily, the current FDA-approved dose. Many of the patients (38%) had received prior treatment with sevelamer and may have grown accustomed to side effects prior to the study, impacting the perception of TEAEs.

Patients who completed this study were eligible for inclusion in a Phase 3, unpublished, long-term extension study where they were treated for an additional 28 weeks (total of 52-56 weeks). This study enrolled 659 subjects, 83.3% of which completed the study. Subjects continued the same treatment they were initially randomized to, however doses ranged from 5-15 g/day in the sucroferric oxyhydroxide group and 2.4-14.4 g/day in the sevelamer group. After 12 months of treatment, the safety profile was comparable between the two treatment groups. The most common adverse events in the sucroferric oxyhydroxide group were gastrointestinal (52.5% in the sucroferric oxyhydroxide group, 42.8% in the SEV group). No deaths were considered related to study treatment. Serum phosphorus levels were maintained over the 28 weeks and were comparable between the two treatment groups.⁹

OTHER NEW TRIAL(S):

Sevelamer was compared to calcium carbonate in a 466 subject randomized, open-label, multicenter study over a 36 months. The primary outcome was cardiovascular death due to arrhythmias in adult patients with CKD stage 5 on dialysis. Patients were recruited from 18 centers in Italy. Subjects were randomized 1:1 to receive sevelamer (n=232) or calcium-containing phosphate binder (n=234), all of which received calcium carbonate. The average baseline serum phosphorus was higher in the sevelamer group (mean, 5.6 ± 1.7 [SD] vs 4.8 ± 1.4 mg/dL). Investigators were allowed to adjust study drug doses in order to reach a target serum phosphorus level of 2.7-5.5 mg/dL. At the end of the study sevelamer had lower serum phosphate levels (4.2 ± 1.2 ; -1.37 ± 1.93 change from baseline; $p < 0.001$) compared to calcium carbonate (4.8 ± 1.1 ; -0.10 ± 1.67 change from baseline; $p = 0.4$). The average median dosage of sevelamer was 4,800 mg/d and 2,000 mg/d of calcium carbonate. Subjects in the sevelamer group had a lower incidence of cardiovascular mortality due to cardiac arrhythmias compared to the calcium carbonate group (HR, 0.06; 95% CI, 0.01-0.25; $P < 0.001$). There were 2 cardiovascular deaths due to cardiac arrhythmias in the sevelamer group and 27 in the calcium carbonate group. The study was limited by the fact that there was a much greater drop in serum phosphorous levels in the sevelamer group, the study was open-labeled, there was a higher baseline coronary artery calcification burden in calcium carbonate-treated patients, and there was a lower than expected mortality rate.¹²

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
Wuthrich, et al. RCT, OL, AC, Phase 2 ¹⁰	Sucroferric oxyhydroxide (SUC): 1.25 g/day 5 g/day 7.5 g/day 10 g/day 12.5 g/day Sevelamer (SEV): 4.8 g/day	Hemodialysis patients with serum phosphorus concentrations >5.5mg/dL n=154	Serum phosphorus after 6 weeks of treatment	<u>Treatment</u> <u>weeks:</u> SUC: 1.25 g/day -0.13 mg/dL (not significant) 5 g/day -1.08 mg/dL (p=0.02) 7.5 g/day -1.25 mg/dL (p=0.003) 10 g/day -2.00 mg/dL (p=0.003) 12.5 g/day -1.69 mg/dL (p=0.003) SEV: 4.8 g/day -1.06 mg/dl (p=0.003)
Floege et al. RCT, OL, AC, Phase 3 ¹¹	Sucroferric oxyhydroxide low dose (LD) vs maintenance dose (MD) sevelamer carbonate studied for secondary endpoint (SEV)	Hemodialysis at least 3x per week or PD for at least 3 months and serum phosphorus concentrations >= 1.94 mmol/l	Change in serum phosphorous from week 24-27	<u>Δ in serum phosphorous from week 24-27</u> LD: +0.6 mmol/l MD: Not reported in study P<0.001 <u>Δ in serum phosphorous at 12 weeks:</u> SUC: -0.71 mmol/l SEV: -0.79 mmol/l P-value not reported
Di Iorio et al. RCT, OL ¹²	Sevelamer Calcium-containing phosphate binder (all patients received calcium carbonate)	Hemodialysis patients that were recruited from 18 centers in Italy.	Cardiovascular death due to cardiac arrhythmias. 24 month intervention phase and patients were followed for 36 months.	<u>CV mortality due to cardiac arrhythmias</u> Sevelamer compared to calcium carbonate (HR, 0.06; 95% CI, 0.01-0.25;P<0.001). <u>Δ in serum phosphorous from baseline:</u> SEV: -1.37 mg/dL P<0.001 Calcium carbonate: -0.1 mg/dL P=0.4

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