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**Month/Year of Review:** September 2012 **Date of Last Review:** September 2010
**PDL Classes:** Phosphate Binders **Source Document:** Provider Synergies

**Current Status of PDL Class:**

- Preferred Agents: CALCIUM ACETATE
- Non-preferred Agents: SEVELAMER (RENAGEL®), SEVELAMER CARBONATE (RENVELA®), 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 effects on bone is unclear.
5. Consider step therapy with calcium acetate first then resin based agents.

**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 2010 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.

**New Systematic Reviews:**
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. [1] Overall, there was no significant reduction in all-cause mortality (10 studies, 3079 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 $mg^2/dL^2$.[2] There was a significant reduction in serum phosphorous (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) was found to be 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 reviewing the effects of calcium-based versus non-calcium based phosphate binders on mortality included a total of eight trials (2873 patients), with 1434 receiving sevelamer (the only non-calcium-based phosphate binder noted in the trials) and 1439 receiving calcium-based phosphate binders.[4] Trials ranged in size from 42 to 2103 subjects with a duration of follow-up between five and 44 months. Three of the studies were rated as high risk of bias, due to inadequate sequence generation, allocation concealment and/or blinding. Two studies were rated as unclear risk of bias because of failure to indicate sequence generation, allocation concealment and/or blinding, and three studies were at low risk of bias. The authors concluded that there was a non-significant reduction in all-cause mortality of 32% (RR 0.68; 95% CI of 0.41-1.11) in favor of non-calcium-based phosphate binders. Only two trials reported information on cardiovascular events, favoring sevelamer (RR 0.85 95% CI 0.35-2.03); although not statistically significant. Authors concluded that they did not find a statistically significant difference in cardiovascular mortality in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders. This meta-analysis was considered good quality according to the AMSTAR tool.[5]

Another good quality meta-analysis compared sevelamer and calcium-based phosphate binders (CBPB) on cardiovascular calcification in hemodialysis (HD) patients.[6] It included 14 trials with a total of 3,271 patients.[6] 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.[7] 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.[6]

**Guidelines:**

Kidney Disease International: Global Outcomes Clinical Practice Guidelines (KDIGO)[8]

The KIDGO Clinical Practice Guidelines from 2009 discuss the use of phosphate binders in CKD. The AGREE II guideline appraisal tool was used to assess the overall quality of the KDIGO guidelines.[9] 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 include the search method utilized (only the Medline search database was used) and the evidence and recommendation connection (some of the recommendations were opinions only due to lack of randomized controlled trials).

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 Trials (Abstracts in Appendix 1):**

**Table 1: Study details**

| Study | Comparison | Population | Primary Outcome | Results |
|---|---|---|---|---|
| Qunibi et al.[10] RCT, DB, PC | Calcium acetate vs. placebo | Nondialyzed patients with GFR<30ml/min/1.73m2 and phosphorous >4.5mg/dl (n=110) | Serum phosphorous at 12 weeks | Serum phosphorous at 12 weeks:<br>Ca: 4.4 ± 1.2 mg/dL<br>Pa: 5.1 ± 1.4 mg/dL<br>P = 0.04<br><br>% with target serum phosphorous:<br>Ca: 59.5%<br>Pl: 36.6%<br>P = 0.04<br><br>Intact parathyroid hormone levels:<br>Ca: 150 ± 157 pg/ml<br>Pa: 351 ± 292 pg/ml<br>P <0.001<br><br>Albumin-adjusted serum calcium:<br>Ca: 9.5 ± 0.8<br>Pa: 8.8 ± 0.8;<br>P <0.001 |
| Gulati, et al.[11] Open-label RCT | Sevelamer vs. calcium acetate | Patients aged 2-18, with CKD stages 3 to 4 (n=22) | Decrease in serum phosphorous after 12 weeks of treatment. | -Patients receiving calcium acetate had a reduction in mean phosphate from 6.6 mg/dl to 5.8 mg/dl at 12 weeks (P = 0.7).<br>-The mean levels of phosphate declined from6.2 mg/dl to 6.0 mg/dl in the sevelamer group (P = 0.2).<br>-There were no significant differences in blood levels of phosphate at 12 weeks between the two groups. |

Definitions used: RCT=randomized controlled trial, DB=double blind, PC=placebo-controlled, GFR=glomerular filtration rate.

**Recommendations:**

1) No further research needed at this time.
2) Evaluate comparative costs for further class decisions.

**Appendix 1: Abstracts of clinical trials**.

*Qunibi W, Winkelmayer WC, Solomon R, Moustafa M, Kessler P, Ho CH, Greenberg J, Diaz-Buxo JA. A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease.*

BACKGROUND: Hyperphosphatemia in patients with chronic kidney disease (CKD) contributes to secondary hyperparathyroidism, soft tissue calcification, and increased mortality risk. This trial was conducted to examine the efficacy and safety of calcium acetate in controlling serum phosphorus in pre-dialysis patients with CKD.

METHODS: In this randomized, double-blind, placebo-controlled trial, 110 nondialyzed patients from 34 sites with estimated GFR < 30 mL/min/1.73 $m^2$ and serum phosphorus > 4.5 mg/dL were randomized to calcium acetate or placebo for 12 weeks. The dose of study drugs was titrated to achieve target serum phosphorus of 2.7-4.5 mg/dL. Serum phosphorus, calcium, iPTH, bicarbonate and serum albumin were measured at baseline and every 2 weeks for the 12 week study period. The primary efficacy endpoint was serum phosphorus at 12 weeks. Secondary endpoints were to measure serum calcium and intact parathyroid hormone (iPTH) levels.

RESULTS: At 12 weeks, serum phosphorus concentration was significantly lower in the calcium acetate group compared to the placebo group (4.4 ± 1.2 mg/dL vs. 5.1 ± 1.4 mg/dL; p = 0.04). The albumin-adjusted serum calcium concentration was significantly higher (9.5 ± 0.8 vs. 8.8 ± 0.8; p < 0.001) and iPTH was significantly lower in the calcium acetate group compared to placebo (150 ± 157 vs. 351 ± 292 pg/mL respectively; p < 0.001). At 12 weeks, the proportions of subjects who had hypocalcemia were 5.4% and 19.5% for the calcium acetate and the placebo groups, respectively, while the proportions of those with hypercalcemia were 13.5% and 0%, respectively. Adverse events did not differ between the treatment groups.

CONCLUSIONS: In CKD patients not yet on dialysis, calcium acetate was effective in reducing serum phosphorus and iPTH over a 12 week period.

*Gulati A, Sridhar V, Bose T, Hari P, Bagga A. Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4. Int Urol Nephrol. 2010 Dec;42(4):1055-62. Epub 2009 Dec 18.*

BACKGROUND: The relative effectiveness and safety of sevelamer, a mineral-free phosphate binder, for treatment of hyperphosphatemia in children with chronic kidney disease is uncertain.

AIM: This study was designed to compare the efficacy and acceptability of sevelamer hydrochloride to calcium acetate as a phosphate binder in pediatric patients with chronic kidney disease.

METHODS: A 12-week open-label trial of sevelamer hydrochloride vs calcium acetate was initiated in 22 patients, aged 2-18, with CKD stages 3 and 4. After a 2-week washout of phosphate binders and vitamin D, patients were randomized to receive sevelamer hydrochloride or calcium acetate. The effect of therapy was adjusted for baseline blood levels of calcium, phosphorus, calcium-phosphate product, alkaline phosphatase, PTH and GFR using ANOVA. The primary end point was the decrease in serum phosphorus levels after 12 weeks of treatment.

RESULTS: Of the 22 patients enrolled, data of 19 patients were used for analysis. The adjusted mean serum phosphate levels at 12 weeks did not differ significantly between calcium acetate- (5.3 mg/dl) and sevelamer-treated subjects (6.1 mg/dl) (P adjusted means = 0.6). The adjusted blood level of calcium at 12 weeks was significantly lower in the sevelamer-treated patients (8.2 mg/dl) compared to those treated with calcium acetate (9.1 mg/dl) (P adjusted means = 0.01). In the sevelamer group, there was a non-significant decrease in serum bicarbonate, whereas the total and LDL cholesterol significantly decreased at 12 weeks (P = 0.04). Sevelamer hydrochloride was well tolerated and without adverse effects related to the drug.

CONCLUSIONS: Compared to calcium acetate, use of sevelamer in children with chronic kidney disease is associated with similar reduction in serum phosphate levels, lower risk of hypercalcemia, and marked decrease in serum lipid levels.

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