Therapeutic Class Overview
Phosphorus Depleters

Therapeutic Class

- **Overview/Summary:** Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (CaxP) product, is associated with an increased risk of vascular, valvular and other soft-tissue calcification in patients with CKD. The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and the administration of phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. There are several different phosphorus binders that are currently available; however, the class can be divided into two subcategories: calcium- and non-calcium-containing products.[1-4] In general, calcium-containing phosphorus binders (Eliphos®, PhosLo®, Phoslyra®) are associated with higher serum calcium and lower serum parathyroid hormone levels compared to the non-calcium-containing products.[5-7] Increased serum calcium levels leads to hypercalcemia and also increases the risk of vascular calcification and arterial disease in CKD patients.[4] As a result, these products are typically avoided in CKD patients with hypercalcemia or severe vascular calcification.[2-4] The available non-calcium-containing phosphorus binders include sevelamer, available in two salt forms (hydrochloride [Renagel®] and carbonate [Renvela®]), lanthanum carbonate (Fosrenol®), ferric citrate (Auryxia®) and sucroferric oxyhydroxide (Velphoro®).[8-10] These products are typically reserved for use in CKD patients with hypercalcemia, or as adjunct to a regimen supplying the maximum allotted dose of elemental calcium from calcium-containing phosphorus binders.[1-4] The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a new, buffered formulation was created. The newer, sevelamer carbonate formulation will most likely be thought of as the preferred formulation of sevelamer because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products.[4]

Table 1. Current Medications Available in the Class[5-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Calcium acetate (Eliphos®*, PhosLo®*, Phoslyra®)	Control hyperphosphatemia in end stage renal failure. Reduce Phosphate with End Stage renal disease (Phoslyra®).	Capsule: 667 mg Oral solution: 667 mg/5 mL Tablet: 667 mg	✔
Ferric citrate (Auryxia®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet: 210 mg	
Lanthanum carbonate (Fosrenol®)	Reduce phosphate with end stage renal disease.	Tablet, chewable: 500 mg 750 mg 1,000 mg Oral Powder: 750 mg 1,000 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sevelamer carbonate (Renvela®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Powder for oral suspension: 0.8 g 2.4 g Tablet: 800 mg	-
Sevelamer hydrochloride (Renagel®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.†	Tablet: 400 mg 800 mg	-
Sucroferric oxyhydroxide (Velphoro®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet, chewable: 500 mg	-

*Generic available in at least one dosage form or strength.
† The safety and efficacy of sevelamer hydrochloride in chronic kidney disease patients who are not on dialysis have not been studied.

Evidence-based Medicine

- The available evidence supports the hypothesis that all of the phosphorus binders (or phosphorus depleters) are efficacious in controlling serum phosphorus levels.[13-54] In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluate surrogate endpoints. In addition, due to ethical concerns regarding a prolonged lack of appropriate treatment, most trials evaluating the newer phosphorus binders against placebo have been short term, with longer trials using calcium-containing binders as the comparator.[1]
- No prospective trials have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level endpoints. Epidemiological data suggests that phosphorus levels above the normal range are associated with increased morbidity and mortality.[1]
- The results of a recent Cochrane Systematic Review by Navaneethan and colleagues demonstrated that there was no statistically significant reduction in all-cause mortality when patients received sevelamer hydrochloride compared to those receiving calcium-based phosphate binders (relative risk, 0.73; 95% confidence interval, 0.46 to 1.16). No comparison of lanthanum carbonate to calcium-containing salts was made.[47]
- Two meta-analyses have been published reviewing the clinical trials of the phosphate binders.[48,49] Tonelli et al compared sevelamer products to any other therapy or placebo in patients with ESRD, on dialysis or who had had a kidney transplant. The pooled analysis showed that phosphate levels with sevelamer was similar or slightly higher than with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19). However, the overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, −0.12 to −0.07).[48] Jamal et al evaluated all-cause mortality and compared calcium-based phosphate binders to non-calcium phosphate binders in patients with chronic kidney disease. The results of this meta-analysis showed that patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR,0.78; 95% CI, 0.61 to 0.98). When non-randomized trials were added to the pooled analysis, the reduction in all-cause mortality was 13% (RR,0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders.[49]
- The safety and efficacy of ferric citrate was established in two clinical trials.[50,51]
    - The demonstrated reductions from baseline to week four in mean serum phosphorus were significantly greater with 6 and 8 grams/day than with 1 gram/day dose (-1.3 mg/dL and -1.5 mg/dL placebo-corrected differences, respectively; P<0.0001).[50]
    - Patients were eligible to enter a four-week, placebo-controlled withdrawal phase if they had been receiving ferric citrate during the 52-week study. During the placebo-controlled period,

the serum phosphorus concentration rose by 2.2 mg/dL in patients receiving placebo compared to patients who remained on ferric citrate (-0.24 mg/dL vs 1.79 mg/dL; P<0.001).[51]

- The safety and efficacy of sucroferric oxyhydroxide was demonstrated in two randomized clinical trials, one six-week, open label, active controlled dose-finding study and one 55-week, active controlled, parallel group, dose-titration and extension study.[12,52-54]
    - In the phase II, dose-finding study, at six weeks, sucroferric oxyhydroxide decreased serum phosphorus compared to baseline in the 5.0, 7.5, 10.0 and 12.5 grams/day arms but not the 1.25 grams/day arm (P≤0.016). A similar decrease to sevelamer hydrochloride was seen in the 5.0 and 7.5 grams/day arms.[1,52]
    - In the after the dose-titration study, serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer throughout the extension study and the difference between groups was not statistically significant (P=0.14).[53,54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Currently available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels. Furthermore, it is generally accepted that no one product is effective and acceptable to every patient.[2,3]
    - Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on chronic kidney disease [CKD] Stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD.
    - It is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.[1]
    - Combination therapy, with multiple binders, may also be an option in order to control serum phosphorus levels while minimizing the side effects associated with any specific binder.[2,3]
    - Phosphorus binders should be utilized in patients with CKD Stages 3 to 5D who cannot adequately maintain serum phosphorus levels within the normal range with dietary phosphorus restriction.[1-3]
    - Choice of product should take into account the Stage of CKD, the presence of other components of CKD-Mineral and Bone Disorder, concomitant therapies and adverse event profiles.[1]
- Other Key Facts:
    - Currently, the calcium-containing products (Eliphos®, PhosLo®) are available generically in tablet and capsule formulations.
    - Calcium acetate (Phoslyra®) is available as an oral solution, and sevelamer carbonate (Renvela®) is available as oral powder for suspension.[7,10]
    - Lanthanum, and sevelamer carbonate/hydrochloride are contraindicated in patients with bowel obstruction, while calcium acetate is contraindicated in hypercalcemia[9-11]
    - Ferric citrate is contraindicated in iron overload syndromes.[8]

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009;76(Suppl 113):S1-130.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42(Suppl 3):S1-202.
3. National Institute for Health and Clinical Excellence. Hyperphosphataemia in chronic kidney disease: management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease. National Institute for Health and Clinical Excellence; London (UK): 2013 Mar. [cited 2014 Aug 18]. Available from: https://www.nice.org.uk/Guidance
4. Quarles LD. Treatment of hyperphosphatemia in chronic kidney disease. In: Bernes JS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2014 Aug 25]. Available from: http://www.utdol.com/utd/index.do.
5. Eliphos® [package insert]. Madison (MS): Hawthorn Pharmaceuticals, Inc.; 2015 Sept.
6. PhosLo® [package insert]. Waltham (MA): Fresenius Medical Care; 2013 Mar.
7. Phoslyra® [package insert]. Waltham (MA): Fresenius Medical Care; 2015 Oct.
8. Auryxia® [package insert]. New York (NY): Keryx Biopharmaceuticals, Inc.; 2016 Mar.

9. Fosrenol® [package insert]. Wayne (PA): Shire US Inc.; 2016 Mar.
10. Renvela® [package insert]. Cambridge (MA): Genzyme Corporation; 2016 Mar.
11. Renagel® [package insert]. Cambridge (MA): Genzyme Corporation; 2016 Mar.
12. Velphoro® [package insert]. Waltham (MA): Fresenius Medical Care; 2014 Sep.
13. Shigematsu T. One year efficacy and safety of lanthanum carbonate for hyperphosphatemia in Japanese chronic kidney disease patients undergoing hemodialysis. Ther Apher Dial. 2010;14(1):12-9.
14. Vemuri N, Michelis MF, Matalon A. Conversion to lanthanum carbonate monotherapy effectively controls serum phosphorus with a reduced tablet burden: a multicenter open-label study. BMC Nephrol. 2011 Sep 30;12:49.
15. Almirall J, Betancourt L, Esteve V, Valenzuela MP, López T, Ruiz A, et al. Clinical usefulness of lanthanum carbonate for serum phosphate control in difficult patients. Int Urol Nephrol. 2012 Feb;44(1):231-6.
16. Finn WF, Joy MS. A long-term, open-label extension study on the safety of treatment with lanthanum carbonate, a new phosphate binder, in patients receiving hemodialysis. Curr Med Res Opin. 2005;21(5):657-64.
17. Hutchison AJ, Barnett ME, Krause R, Kwan JTC, Siami GA. Long-term efficacy and safety profile of lanthanum carbonate: results for up to six years of treatment. Nephron Clin Pract. 2008;110:c15-23.
18. Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a six-month, randomized, comparative trial vs calcium carbonate. Nephron Clin Pract. 2005;100:c8-19.
19. Finn WF, Joy MS, Hladik G, Lanthanum Study Group. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis (abstract). Clin Nephrol. 2004;62(3):193-201.
20. Joy MS, Finn WF. Randomized, double-blind, placebo-controlled, dose-titration, Phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. Am J Kid Dis. 2003;42:96-107.
21. Sprague SM, Abboud H, Qiu P, Dauphin M, Zhang P, Finn W. Lanthanum carbonate reduces phosphorus burden in patients with CKD Stages 3 and 4: a randomized trial. Clin J Am Soc Nephrol. 2009;4:178-85.
22. Shigematsu T. Lanthanum carbonate effectively controls serum phosphate without affecting serum calcium levels in patients undergoing hemodialysis. Ther Apher Dial. 2008;12(1):55-61.
23. Al-Baaj F, Speake M, Hutchison AJ. Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. Nephrol Dial Transplant. 2005;20:775-82.
24. Mehrotra R, Martin KJ, Fishbane S, Sprague SM, Zeig S, Anger M, et al. Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: a multicenter study. Clin J Am Soc Nephrol. 2008;3:1437-45.
25. Ketteler M, Rix M, Fan S, Pritchard N, Oestergaard O, Chasan-Taber S, et al. Efficacy and tolerability of sevelamer carbonate in hyperphosphatemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol. 2008;3:1125-30.
26. Fischer D, Cline K, Plone MA, Dillon M, Burke AK, Blair AT. Results of a randomized crossover study comparing once-daily and thrice-daily sevelamer dosing. Am J Kidney Dis. 2006;48:437-44.
27. Ouellet G, Cardinal H, Mailhot M, Ste-Marie LG, Roy L. Does concomitant administration of sevelamer and calcium carbonate modify the control of phosphatemia? Ther Apher Dial. 2009;14(2):172-7.
28. Iwasaki Y, Takami H, Tani M, Yamaguchi Y, Goto H, Goto Y, et al. Efficacy of combined sevelamer and calcium carbonate therapy for hyperphosphatemia in Japanese hemodialysis patients. Ther Apher Dial. 2005;9(4):347-51.
29. Qunibi WY, Hootkins RE, McDowell LL, Meyer MS, Simon M, Garza RO, et al. Treatment of hyperphosphatemia in hemodialysis patients: the Calcium Acetate Renagel Evaluation (CARE Study). Kidney Int. 2004;65:1914-26.
30. Finn WF, SPD 405-307 Lanthanum Study Group. Lanthanum carbonate vs standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients (abstract). Clin Nephrol. 2006;65(3):191-202.
31. Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a two-year comparative study of lanthanum carbonate vs standard therapy. Current Medical Research & Opinion. 2009;25(12):3021-8.
32. Hutchison AJ, Maes B, Vanwallegham J, Asmus G, Mohamed E, Schmieder R, Backs W, Jamar R, Vosskuhler A. Long-term efficacy and tolerability of lanthanum carbonate: results from a three-year study. Nephron Clin Pract. 2006;102:c61-71.
33. Kasai S, Sato K, Murata Y, Kinoshita Y. Randomized crossover study of the efficacy and safety of sevelamer hydrochloride and lanthanum carbonate in Japanese patients undergoing hemodialysis. Ther Apher Dial. 2012 Aug;16(4):341-9.
34. Delmez J, Block G, Robertson J, Chasan-Taber S, Blair A, Dillon M, et al. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis (abstract). Clin Nephrol. 2007;68(6):386-91.
35. Fan S, Ross C, Mitra S, Kalra P, Heaton J, Hunter J, et al. A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease in patients on haemodialysis. Nephrol Dial Transplant. 2009;24:3794-9.
36. Fishbane S, Delmez J, Suki WN, Hariachar SK, Heaton J, Chasan-Taber S, et al. A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. Am J Kidney Dis. 2010;55:307-15.
37. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, et al. Effects of sevelamer and calcium-based phosphate binders on morality in hemodialysis patients. Kidney Int. 2007;72:1130-7.
38. St. Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. Am J Kidney Dis. 2008;51:445-54.
39. Pieper AK, Haffner D, Hoppe B, Dittrich K, Offner G, Bonzel KE, et al. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. Am J Kidney Dis. 2006;47:625-35.

40. Evenepoel P, Selgas R, Caputo F, Foggensteiner L, Heaf JG, Ortiz A, et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. Nerphrol Dial Transplant. 2009;24:278-85.
41. Hervas JG, Prados D, Cerezo S. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate. Kidney Int. 2003;63(85):S69-72.
42. Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in haemodialysis patients. Am J Kidney Dis. 1999;33(4):694-701.
43. Xu J, Zhang YX, Yu XQ, Liu ZH, Wang LN, et al. Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China. BMC Nephrol. 2013 Feb 4;14:29. doi: 10.1186/1471-2369-14-29.
44. Ando R, Kimura H, Sato H, Iwamoto S, Yoshizaki Y, et al. Multicenter study of long-term (two-year) efficacy of lanthanum carbonate. Ther Apher Dial. 2013 Apr;17 Suppl 1:2-8. doi: 10.1111/1744-9987.12046.
45. Gotoh J, Kukita K, Tsuchihashi S, Hattori M, Iida J, et al. Study of prolonged administration of lanthanum carbonate in dialysis patients. Ther Apher Dial. 2013 Apr;17 Suppl 1:9-14. doi: 10.1111/1744-9987.12043.
46. Takeuchi K, Matsuda E, Sekino M, Hasegawa Y, Kamo Y, et al. Three-year follow-up of lanthanum carbonate therapy in hemodialysis patients. Ther Apher Dial. 2013 Apr;17 Suppl 1:15-21. doi: 10.1111/1744-9987.12045.
47. Navaneethan SD, Palmer SC, Vecchio M, Craig JC, Elder GJ, Strippoli GF. Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD006023.
48. Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, et al. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrol Dial Transplant. 2007 Oct;22(10):2856-66.
49. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013 Oct 12;382(9900):1268-77. doi: 10.1016/S0140-6736(13)60897-1. Epub 2013 Jul 19.
50. Dwyer JP, Sika M, Schulman G, Chang IJ, Anger M, Smith M, et al. Dose-response and efficacy of ferric citrate to treat hyperphosphatemia in hemodialysis patients: a short-term randomized trial. Am J Kidney Dis. 2013 May;61(5):759-66. doi: 10.1053/j.ajkd.2012.11.041. Epub 2013 Jan 29.
51. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT et al. Ferric Citrate Controls Phosphorus and Delivers Iron in Patients on Dialysis. J Am Soc Nephrol. 2015 Feb;26(2):493-503. doi: 10.1681/ASN.2014020212. Epub 2014 Jul 24.
52. Wüthrich RP, Chonchol M, Covic A, Gaillard S, Chong E, Tumlin JA. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. Clin J Am Soc Nephrol. 2013 Feb;8(2):280-9. doi: 10.2215/CJN.08230811. Epub 2012 Nov 2.
53. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney Int. 2014 Mar 19. doi: 10.1038/ki.2014.58.
54. Floege J, Covic AC, Ketteler M, Mann JF, Rastogi A, Spinowitz B, et al. Long-term effects of iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. Nephrol Dial Transplant. 2015 Feb 16. pii: gfv006. [Epub ahead of print]