



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: Phosphate Binders**  
**-February 2018-**



**Background:**

Chronic kidney disease is a highly prevalent condition in the U.S. population, most commonly resulting from diabetes mellitus and/or hypertension.<sup>1</sup> Hyperphosphatemia in chronic kidney disease (CKD) is common, especially among dialysis patients. According to data from the 2016 U.S. Renal Data System, the prevalence is 37% for hemodialysis patients and 42% for peritoneal dialysis patients.<sup>2</sup> Among people with CKD, hyperphosphatemia results from a reduction in the filtered phosphate load owing to declining glomerular filtration. In February 2018, the NPTC undertook a comprehensive review of calcium-based and non-calcium based phosphate binders. As a result of this review, the NPTC **removed the restriction for a branded sevelamer product** and **retained sevelamer carbonate** on the IHS National Core Formulary, along with oral calcium preparations.

**Discussion:**

There are multiple aspects of phosphate homeostasis in humans, including dietary consumption and intestinal absorption of phosphate, the balance of bone formation and resorption where bone serves as a phosphate reservoir, and the elimination of phosphate primarily from the kidneys.<sup>3</sup> A variety of reasons have been used by clinicians to justify treatment of hyperphosphatemia, including to decrease the risks of bone and mineral disorder, fractures, cardiovascular disease, progression of CKD, and mortality. For example, two studies analyzed from the U.S. Renal Data System showed an association with mortality risk for both increased serum phosphate (serum phosphate >6.5, mortality RR: 1.27) and the calcium phosphate product.<sup>4</sup> However, these and other studies showing association between increased serum phosphate levels and mortality have been observational or cohort studies. To date, there have been no prospective randomized trials evaluating the effects of varying phosphorus concentration targets on clinical outcomes.

The foundation of all hyperphosphatemia treatment strategies in CKD is dietary phosphate restriction. However, this is often limited both by the complexity of the dietary regimen and the protein needs of the patient. For patients with end stage renal disease, the elimination of phosphate may be enhanced with dialysis. However, conventional dialysis is commonly limited by rebound hyperphosphatemia. Pharmacotherapy may aid in treatment of hyperphosphatemia through reduction in intestinal absorption.

Historically, in the late 1980s, calcium-based phosphate binders were the treatment of choice for the management of hyperphosphatemia in patients with CKD, replacing aluminum-based binders. The mechanism of phosphate lowering is through intestinal combination with dietary phosphate to form insoluble calcium phosphate which is excreted in feces. Concerns have been raised about the potential link between calcium-based phosphate binders and morbidity and mortality, especially in dialysis patients. Cardiovascular disease remains the leading cause of death in dialysis patients, and the problem of vascular calcification, especially coronary artery calcification, has been observed in post-mortem analyses of even young dialysis patients without traditional cardiovascular risk factors. This led to the development of non-calcium-based phosphate binders, including sevelamer and lanthanum.

A variety of comparative effectiveness studies have been completed in the phosphate binder class. In 2013, a systematic review and network meta-analysis was published to determine comparative effectiveness of calcium-based versus non-calcium-based phosphate binders in patients with CKD. The results indicated a 22% reduction in all-cause mortality (RR 0.78, 95% CI: 0.61-0.98) with non-calcium based phosphate binders compared to calcium-based phosphate binders, with moderate heterogeneity among the included trials.<sup>5</sup> The authors concluded that non-calcium-based phosphate binders are associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders in patients with CKD.

In 2016, a systematic review and network meta-analysis was published to determine comparative effectiveness of phosphate binders in patients with CKD and mineral bone disease. This meta-analysis compared calcium-based phosphate binders, non-calcium-based phosphate binders, phosphorous restricted diet, placebo, or no treatment on outcomes including all-cause mortality, cardiovascular mortality, and hospitalization. Results included higher mortality with calcium than sevelamer (RR 1.89, 95% CI: 1.02-3.50) or a composite of non-calcium-based phosphate binders (RR 1.76, 95% CI: 1.21-2.56), no difference in cardiovascular mortality between calcium- and non-calcium-based phosphate binders (RR 2.54, 95% CI: 0.67-9.62), and a non-significant trend towards higher hospitalization with calcium- than non-calcium-based phosphate binders (RR 1.29, 95% CI: 0.94-1.74).<sup>6</sup>

The most recent update of the [Kidney Disease, Improving Global Outcomes clinical practice guideline](#) for the management of mineral and bone disease was published in July 2017.<sup>7</sup> In recognition of the interdependency of biochemical markers, including phosphate, calcium, and parathyroid hormone as well as variations resulting from factors such as diet, medication adherence, time since dialysis, and diurnal variation, it was recommended that treatment decisions be based on serial assessments of the markers, when taken together. Similarly, treatment decisions regarding hyperphosphatemia should be based on trends, such as progressively or persistently elevated serum phosphate. *Because of the observed relationship between hyperphosphatemia and mortality, as well as the lack of proven treatment-based improvement in patient centered outcomes, the guidelines committee adjusted prior guidance with the goal to lower elevated phosphate levels **toward** normal.* Limitation in dietary phosphate intake is recommended as integral to any treatment plan for moderate or advanced CKD, either alone or in combination with other treatment modalities such as use of phosphate binders or dialysis. Finally, a recommendation was made to restrict the dose, on an individualized basis, of calcium-based phosphate binders in keeping with an observed mortality benefit.

Part of the basis for this latter recommendation was a pair of pilot studies comparing sevelamer and calcium-based phosphate binders with regard to mortality. The first pilot study enrolled 212 outpatients with hyperphosphatemia and stage 3 to 4 CKD who were then randomized to sevelamer or calcium carbonate.<sup>8</sup> This was a randomized, multicenter, non-blinded study with a three year follow up. The all-cause mortality rate was significantly higher among patients receiving calcium carbonate (HR 0.45, 95% CI: 0.23-0.91). With regard to event-free survival from the composite endpoint (all-cause mortality and dialysis inception) among patients treated either with sevelamer or calcium carbonate, survival was significantly worse among patients receiving calcium carbonate (HR 0.52, 95% CI: 0.35-0.76). There was also a non-significant trend for dialysis inception alone, which was more favorable in the sevelamer-treated group (HR 0.55, 95% CI: 0.35-0.88). The authors concluded that sevelamer provided benefits, particularly with regard to both all-cause mortality and the composite endpoint.

A follow-up study enrolled 466 hemodialysis patients who were randomized to either sevelamer or calcium carbonate.<sup>9</sup> For the primary endpoint of cardiovascular death due to arrhythmia, sevelamer-treated patients had a significantly lower rate (HR 0.06, 95% CI: 0.01-0.25) compared to hemodialysis patients treated with a calcium-based phosphate binder. A similar result was also seen for secondary outcomes, including all-cause cardiovascular mortality and all-cause mortality. The authors concluded that sevelamer, when compared to a calcium-based phosphate binder, improves survival in hemodialysis patients. Furthermore, since no phosphate binder type has been demonstrated to reduce mortality compared with no treatment, standard care, or placebo in clinical trials, it should be noted that none of these studies can determine whether the lower mortality rate with sevelamer (compared with calcium-based phosphate binders) represents a superior sevelamer effect or harm from calcium-based phosphate binders or both.

#### **Findings:**

Hyperphosphatemia is common among patients with moderate to severe CKD. Phosphate homeostasis and related patient outcomes in CKD is impacted by multiple variables which should influence treatment decisions. Hyperphosphatemia in CKD is linked to higher mortality in observational and cohort studies. Use of calcium based binders in CKD should be dose-restricted on an individualized basis due to the observed association with increased mortality. Comparative effectiveness data for various phosphate binders is inconclusive regarding superiority of a specific agent or agents as limited by study design.

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If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).

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