September 10, 2007

Cathy A Miller, MPH, RN
FDA Advisors and Consultants Staff (ACS)
HFD-21, Room 1099
5630 Fishers Lane
Rockville, MD 20857

Re: Renagel® (sevelamer hydrochloride) 400, 800mg Tablets, NDA 21-179
    Phoslo® (calcium acetate) 667 mg GelsCaps, NDA 21-160
    Fosrenol® (lanthanum carbonate) 250, 500, 750, 1000 mg Tablets,
    NDA 21-468

    Briefing Document for October 16, 2007 Advisory Committee Meeting

Dear Ms. Miller:

This submission contains the fully releasable briefing document compiled by Genzyme Corporation, Fresenius Medical Care North America, and Shire Pharmaceuticals for use at the October 16, 2007 Cardiovascular and Renal Products Advisory Committee Meeting. This document is available for public disclosure without redaction. As requested in the letter dated July 17, 2007, 25 hardcopies and 25 electronic copies of the briefing document are included. As previously discussed with Alisea Crowley and Cicely Reese, the references are being submitted as electronic copies only and are contained on CDs separate from the fully releasable briefing document. This completes the required submission of the shared briefing document by the three companies listed above. Genzyme, Shire and Fresenius will also submit copies of the briefing document to our own respective NDAs.

Please contact me should you have any questions.

Sincerely,

Mary Beth Clarke
Senior Director, Regulatory Affairs

Phone: 617-768-6907
Phosphate Binders for Treatment of Hyperphosphatemia in Patients with Chronic Kidney Disease

BRIEFING DOCUMENT

Advisory Committee Meeting of the Cardiovascular and Renal Drugs Division of the US Food and Drug Administration

October 16, 2007

Fresenius Medical Care
920 Winter Street
Waltham, MA 02451-1457

Genzyme Corporation
500 Kendall Street
Cambridge, Massachusetts 02142

Shire Pharmaceuticals
725 Chesterbrook Boulevard
Wayne, Pennsylvania 19087

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION
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<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>BMP</td>
<td>bone morphogenetic protein</td>
</tr>
<tr>
<td>Ca × P</td>
<td>calcium-phosphate product</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CAC</td>
<td>coronary artery calcification</td>
</tr>
<tr>
<td>CARE</td>
<td>Cholesterol and Recurrent Events Study (Tonelli, Sacks, 2005, <em>Circulation</em>)</td>
</tr>
<tr>
<td>Cbfa-1</td>
<td>core binding factor α-1</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CKD-MBD</td>
<td>chronic kidney disease-mineral and bone disorder</td>
</tr>
<tr>
<td>CMAS</td>
<td>Case Mix Adequacy Study</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>CUA</td>
<td>calcific uremic arteriopathy</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DDMS</td>
<td>Dialysis Morbidity and Mortality Study</td>
</tr>
<tr>
<td>DOPPS</td>
<td>Dialysis Outcomes and Practice Patterns Study</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
<tr>
<td>ESKD</td>
<td>end-stage kidney disease</td>
</tr>
<tr>
<td>FAHR</td>
<td>fully-adjusted hazard ratio</td>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>FGF</td>
<td>Fibroblast growth factor</td>
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<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<tr>
<td>HPT</td>
<td>hyperparathyroidism</td>
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<tr>
<td>HPTH</td>
<td>hyperparathyroidism bone disease</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>iPTH</td>
<td>intact parathyroid hormone</td>
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<tr>
<td>KDIGO</td>
<td>Kidney Disease Improving Global Outcomes</td>
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<tr>
<td>KDOQI</td>
<td>Kidney Dialysis Outcome Quality Initiative</td>
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<tr>
<td>K/DOQI</td>
<td>Kidney Dialysis Outcome Quality Initiative</td>
</tr>
<tr>
<td>KEEP</td>
<td>Kidney Early Evaluation Program (of the NKF)</td>
</tr>
<tr>
<td>LVMI</td>
<td>Left ventricular mass index</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<td>MGP</td>
<td>Matrix GLA protein</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
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<tr>
<td>NKF</td>
<td>National Kidney Foundation</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>Npt2b</td>
<td>A Na-phosphate cotransporter</td>
</tr>
<tr>
<td>OPN</td>
<td>Osteopontin</td>
</tr>
<tr>
<td>Pit-1</td>
<td>sodium-dependent phosphate cotransporter</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>PTX</td>
<td>parathyroidectomy</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>USRDS</td>
<td>United States Renal Data System</td>
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<tr>
<td>VSMC</td>
<td>Vascular Smooth Muscle Cells</td>
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</table>
1. EXECUTIVE SUMMARY

The Cardiovascular and Renal Drugs Division of the US Food and Drug Administration (FDA) is convening an advisory committee meeting (October 16, 2007) to discuss regulatory considerations for extending the use of phosphate binders from the dialysis population to the pre-dialysis population. The FDA has invited three companies that currently market phosphate binders (Fresenius Medical Care, Genzyme Corporation, and Shire Pharmaceuticals) to participate in the advisory committee discussions, to provide a joint briefing package, and to make presentations to the committee members.

The currently approved phosphate binders include calcium acetate (PhosLo\textsuperscript{1}), lanthanum carbonate (Fosrenol\textsuperscript{2}), and sevelamer hydrochloride (Renagel\textsuperscript{3}), which were approved on the basis of evidence that they control phosphorus levels in patients with chronic kidney disease (CKD) on dialysis. These drugs bind phosphate in the gastrointestinal tract to decrease absorption and thereby reduce the body burden of phosphate. Each compound is presently indicated for reduction of serum phosphorus in CKD patients on dialysis only. Given that CKD progresses as a continuum, with subtle clinical distinctions between pre-dialysis and dialysis, the three companies believe that no distinction should be made regarding the treatment of hyperphosphatemia in CKD patients based on their dialysis status.

All three companies believe that there is ample evidence to support earlier phosphate binder treatment of CKD patients, and that failure to do so is not in the best interest of patients. This position is consistent with the National Kidney Foundation’s (NKF) current Kidney Dialysis Outcome Quality Initiative (KDOQI) guidelines (NKF, 2003, \textit{Am J Kidney Dis}) recommending early detection and intervention in the treatment of elevated serum phosphorus in patients with CKD. The objective of this briefing package is to summarize existing data indicating the following:

- Phosphate imbalance precedes the need for dialysis in CKD, and should be treated at the time hyperphosphatemia begins.
- The clinical consequences of not treating hyperphosphatemia prior to initiation of dialysis include bone disorders, vascular calcification, and progression of renal disease.
- Hyperphosphatemia is an independent risk factor for cardiovascular morbidity and mortality, and for the progression of renal failure in the pre-dialysis population.

\textsuperscript{1} PhosLo\textsuperscript{1} is a registered trademark of Fresenius Medical Care North America
\textsuperscript{2} Fosrenol\textsuperscript{2} is a registered trademark of Shire Pharmaceuticals
\textsuperscript{3} Renagel\textsuperscript{3} is a registered trademark of Genzyme Corporation
Vascular calcification is associated with increased atherosclerotic morbidity and mortality and is irreversible.

- The risk of appropriate early treatment of hyperphosphatemia in CKD patients not on dialysis is minimal compared to the benefits of preventing mineral metabolism abnormalities in CKD.

It is known that phosphate binders are being prescribed presently for patients with hyperphosphatemia who are not on dialysis. An important goal of label expansion is to ensure that these patients are receiving access to the best possible care by providing a labeled indication for the informed treatment of hyperphosphatemia in CKD patients prior to and following initiation of dialysis.

There is considerable collective experience with lanthanum carbonate, calcium acetate, and sevelamer hydrochloride in CKD patients on dialysis: The total estimated patient exposure to lanthanum carbonate, as of 30 June 2007, is in excess of 26,762 patient-years; total estimated patient exposure to calcium acetate, as of June 2007, is greater than 375,000 patient-years; and a total of 305,427 patients received sevelamer hydrochloride from October 2004 to October 2005 alone. Thus, the risks of the currently available phosphate binders are well characterized in more severe CKD patients on dialysis. The extensive exposure of all phosphate binders in patients on dialysis, in conjunction with the well characterized adverse drug reaction profile, demonstrates that the risks expected for use in pre-dialysis CKD patients with hyperphosphatemia will be small compared to the morbidity and mortality observed with this patient population.

Patients with CKD frequently have comorbid conditions. As reported in the 2006 United States Renal Data System (USRDS) Annual Report, 70% of CKD patients age 50 or older who are covered by employer group health plans have concurrent diagnoses of diabetes, hypertension, or both; an astounding 90% of Medicare CKD patients have diabetes, hypertension, or both. Not surprisingly, a large proportion of these patients also have congestive heart failure. CKD patients therefore represent a clinically complex and challenging patient population. This degree of complexity draws into question the ability to unambiguously and definitively draw inferences from clinical trials designed to examine a single therapeutic intervention. It has been estimated that correction of hyperphosphatemia in CKD patients could save approximately 34,000 patient life-years in the US alone over a 5-year period. All three companies continue to study the effect of phosphate binders on discrete markers of renal function, cardiovascular disease (CVD), and bone and mineral metabolism. However, the clinical disposition of these patients should provide sufficient
rationale against requiring long outcome trials as a prerequisite to expansion of the current indication of phosphate binders to include CKD patients not on dialysis.

Synopsis of Individual Sections

To facilitate discussion, this briefing package is organized into six sections: Background of CKD; Mineral Balance Physiology and Pathophysiology; Clinical Consequences of Hyperphosphatemia; Current Treatment; Evaluation of Risks and Benefits of Treatment of Hyperphosphatemia with Phosphate Binders in CKD Patients Not on Dialysis; and Conclusions. These sections are summarized as follows:

Background of CKD

CKD is a progressive disease in which, over time, the filtering capacity of the kidney continually diminishes until renal replacement therapy is required. The proportion of the US population affected by CKD is estimated at 10%, a number projected to increase in concordance with an aging population that is increasingly affected by diabetes, obesity, and hypertension. A subset of this population have hyperphosphatemia and secondary hyperparathyroidism. CKD is classified (Stages 1-5) on the basis of the presence of kidney damage and the glomerular filtration rate (GFR). Although convenient for diagnostic purposes, these discrete definitions of CKD stages may lead to a lack of understanding that CKD is a continuum. This is supported by the fact that until recently, attention has been focused almost exclusively on those patients with severe CKD requiring dialysis (Stage 5) when in fact there are subtle clinical distinctions between pre-dialysis and dialysis states with evidence for advantages of certain therapeutic interventions prior to the need for dialysis. CKD is associated with a variety of complex metabolic and bone abnormalities that together encompass a syndrome defined in 2006 as CKD-Mineral and Bone Disorder (MBD). Hyperphosphatemia and secondary hyperparathyroidism are implicated as central components in CKD-MBD. Hyperphosphatemia is now recognized as an independent risk factor for CVD in patients with CKD. Hyperphosphatemia manifests prior to CKD Stage 5 thereby affording an opportunity for therapeutic intervention prior to progression to renal replacement therapy. Current NKF guidelines recommend early identification and treatment of hyperphosphatemia in patients with CKD.

Mineral Balance Physiology and Pathophysiology

Phosphorus homeostasis becomes compromised progressively as kidney function declines since the kidneys maintain total body phosphorus balance by modulating the amount of phosphorus excreted daily in the urine. Plasma phosphorus represents less than 1% of total
body phosphate content and in healthy adults, plasma phosphorus levels range from 2.5 to 4.5 mg/dL. Multiple hormonal systems help control serum phosphorus concentrations. One system is mediated in part by 1,25(OH)₂ vitamin D (calcitriol) which promotes phosphorus and calcium absorption across the gastrointestinal tract acting through the Na-phosphate cotransporter Npt2b in the intestinal epithelial cells. Parathyroid hormone (PTH) is a potent modifier of renal phosphorus excretion, and increases urinary phosphorus by blocking phosphate reabsorption in the proximal tubule through its action on Npt2a. PTH also concomitantly increases 1α-hydroxylation of calcitriol, thus raising levels of calcitriol. The second system is mediated by the phosphatonin fibroblast growth factor 23 (FGF-23), a phosphate-regulating protein which reduces conversion of calcidiol to calcitriol. These systems are interdependent upon each other.

Fractional excretion of phosphorus increases gradually and significantly from CKD Stages 1 to 5 to maintain balance. Sometimes in CKD Stage 3 and often in CKD Stages 4 and 5, significant positive phosphorus imbalance will occur as the kidney fails to excrete the absorbed phosphate load. Therefore, hyperphosphatemia is a hallmark of advanced CKD. The pathophysiological consequences of abnormalities in phosphate homeostasis include renal osteodystrophy (currently divided into low and high turnover bone disease). With low bone turnover bone disease, excess phosphorus goes into heterotopic sites, such as the kidney and cardiovascular systems. With high bone turnover bone disease, excessive resorption of bone releases phosphorus and calcium into the circulation, aggravating hyperphosphatemia and causing hypercalcemia. Hyperphosphatemia, vitamin D deficiency, and secondary hyperparathyroidism are predictable consequences of the progressive decline in GFR in patients with CKD.

Clinical Consequences of Hyperphosphatemia

CKD is a complex systemic disease encompassing a continuum of clinical features of increasing severity, including progressively reduced GFR, kidney failure up to and including the need for dialysis, abnormal mineral metabolism and serum mineral levels, and disordered bone metabolism and extraskeletal calcification.

One of the earliest manifestations of CKD is the failure to regulate phosphorus balance, which occurs as part of the complex systemic disorder of mineral and bone metabolism associated with CKD. Marked increases in mean phosphorus levels have been reported when GFR levels declined by 50%, fell below 30 mL/min/1.73 m² (Stage 4), or reached CKD Stage 5 CKD.
In the CKD population not on dialysis, the morbidity and mortality rates are greatly elevated and are related proportionately to the level of renal impairment.

- **Hyperphosphatemia and Bone Disease**

Considerable evidence now exists to support an association of metabolic consequences of hyperphosphatemia, most notably secondary hyperparathyroidism, with bone disease. Evidence of bone disease appears relatively early in CKD, with histological changes occurring at GFR <60 mL/min/1.73 m². Abnormal bone morphology in patients with CKD can lead to fractures, deformities, and bone pain. Hyperphosphatemia is associated with fracture-related hospitalization as a result of impaired bone quality in CKD.

- **Hyperphosphatemia and Cardiovascular Disease**

Cardiovascular Disease (CVD) is a major cause of death among patients with CKD both before and after they progress to Stage 5 and dialysis, with almost half of all deaths on dialysis due to cardiovascular events. Among CKD patients, CVD is twice as common and advances at twice the rate compared with non-CKD patients. CVD advances at a similarly higher rate in CKD patients who die and those who survive to end-stage renal disease (ESRD).

There are traditional and uremia-related risk factors that contribute to the increased incidence of cardiovascular events in CKD patients. Key among the uremia-related risk factors for CVD morbidity and mortality is hyperphosphatemia, which arises from phosphorus imbalance.

Hyperphosphatemia is involved in the pathogenesis of vascular calcification, an active process that begins in early stages of CKD, is accelerated in CKD Stage 5, and established in many patients at the time of initiation of maintenance dialysis therapy. The presence of vascular calcification, as measured by electron-beam computed tomography, confirms the presence of atherosclerotic plaque and lesions with stenosis. Thus, disordered mineral metabolism with vascular calcification contributes to the progression of atherosclerosis and cardiovascular events in CKD patients.
The following studies discuss the relationship of CKD with the presence of hyperphosphatemia and vascular calcification:

Table 1-1  
**Serum Phosphorus Levels and Vascular Calcification**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Russo, Corrao, 2007, <em>Am J Nephrol</em>)</td>
<td>CKD Stages 3-5 pre-dialysis Normal renal function</td>
<td>113</td>
<td>Coronary artery calcification (CAC) progression was significantly prominent in 51% of CKD patients ($p&lt;0.0001$). Although no association was observed between the clinical and biochemical variables and the total rates of CAC progression, rates above 75th percentile were significantly correlated with higher serum phosphorus levels despite a majority of the patients having “normal” levels of phosphorus according to KDOQI ($p=0.015$).</td>
</tr>
<tr>
<td>(Tomiyama, Higa, 2006, <em>Nephrol Dial Transplant</em>)</td>
<td>CKD (CrCl 15-90 mL/min/1.73m²)</td>
<td>96</td>
<td>Higher levels of serum phosphorus were correlated with the presence of severe CAC (CAC score &gt; 400 Agatson units). Severe CAC were significantly associated with higher levels of phosphorus but not iPTH.</td>
</tr>
<tr>
<td>(Sigrist, Bungay, 2006, <em>Nephrol Dial Transplant</em>)</td>
<td>CKD Stage 4 pre-dialysis Dialysis</td>
<td>134</td>
<td>Arterial calcification had begun in almost 50% of patients prior to initiation of dialysis, but no relationship between serum Pi, corrected calcium, iPTH or phosphate binder type or dose and degree of calcification. A possible explanation for their findings is that their patients had good mineral control and were receiving phosphate binders.</td>
</tr>
<tr>
<td>(Dellegrottaglie, Saran, 2006, <em>Am J Cardiol</em>)</td>
<td>CKD Stages 3-5 pre-dialysis (eGFR &lt; 50 mL/min/1.73m²)</td>
<td>106</td>
<td>Approximately 69% of patients exhibited some CAC. More than 37% had CAC scores above 75th percentile for age- and gender-matched subjects without CKD. Approximately 5% had CAC scores above 90% percentile.</td>
</tr>
<tr>
<td>(Russo, Palmiero, 2004, <em>Am J Kidney Dis</em>)</td>
<td>CKD Stages 2-5 pre-dialysis Normal renal function</td>
<td>140</td>
<td>Serum phosphorus levels were above KDOQI goals in patients with Stages 2-4 CKD and CAC was found to be already present in the early phases of CKD.</td>
</tr>
</tbody>
</table>
The following studies discuss the relationship of CKD with the presence of hyperphosphatemia with or without vascular calcification and its association with cardiovascular events:

### Table 1-2  Association of Serum Phosphorus Levels with Vascular Calcification and Cardiovascular Events

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Tonelli, Sacks, 2005, <em>Circulation</em>) <em>(Cholesterol and Recurrent Events, CARE)</em></td>
<td>Non-CKD Prior coronary disease</td>
<td>4,127</td>
<td>Statistically significant graded association with higher phosphorus levels and the risk of death and cardiovascular events in individuals with prior myocardial infarction, most of whom had serum phosphorus levels within the normal range. Those with serum phosphorus levels $\geq 4$ mg/dL had a 43% risk for developing heart failure, 50% risk for experiencing myocardial infarction, and 32% risk for experiencing the composite outcome of coronary death or nonfatal myocardial infarction compared to those with serum phosphorus of 2.5 to 3.4 mg/dL.</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, <em>J Am Soc Nephrol</em>)</td>
<td>CKD predialysis</td>
<td>6,730</td>
<td>Each 1-mg increment was associated with a 35% increased risk for myocardial infarction, and a 28% increase in risk for the combined endpoint of death and non-fatal myocardial infarction.</td>
</tr>
</tbody>
</table>
-Hyperphosphatemia and Progression of Renal Disease

A body of evidence, summarized in Table 1-3 and presented in more detail in this document, supports a direct association between hyperphosphatemia and progression of renal disease, clinical renal events, and mortality.

Table 1-3  Serum Phosphorus Levels and Progression of Renal Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Voormolen, Noordzij, 2007, Nephrol Dial Transplant) (PREPARE)</td>
<td>CKD pre-dialysis (eGFR 13 mL/min/1.73m²)</td>
<td>547</td>
<td>High serum phosphorus is associated with more rapid decline in renal function.</td>
</tr>
<tr>
<td>(Sigrist, Bungay, 2006, Nephrol Dial Transplant)</td>
<td>CKD Stages 1-5</td>
<td>985</td>
<td>High serum phosphorus is associated with progression to CKD Stage 5 and doubling of serum Cr in a graded fashion.</td>
</tr>
<tr>
<td>(Norris, Greene, 2006, J Am Soc Nephrol) (AASK)</td>
<td>CKD (GFR 20-65 mL/min/1.73m²)</td>
<td>1,094</td>
<td>Elevated serum phosphorus was significantly associated with an increased risk for a decline in GFR by 50% or 25 mL/min/1.73m² or progression to ESRD.</td>
</tr>
<tr>
<td>(Dellegrottaglie, Saran, 2006, Am J Cardiol)</td>
<td>CKD Stages 3-5 predialysis (eGFR &lt; 50 mL/min/1.73m²)</td>
<td>106</td>
<td>Even though the extent of CAC in pre-dialysis CKD patients was not to indices of abnormal renal function or progression in renal dysfunction, higher serum Pi, iPTH, and diabetes status were significantly associated with decreasing renal function (p=0.035).</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, J Am Soc Nephrol)</td>
<td>CKD pre-dialysis</td>
<td>6,730</td>
<td>Marked increases in mean phosphorus levels when GFR levels fell below 30 mL/min/1.73 m² (Stage 4).</td>
</tr>
</tbody>
</table>

-Hyperphosphatemia and Mortality

Phosphorus retention or increased body burden, up to and including hyperphosphatemia, has emerged as an important risk factor for mortality in the CKD population, both as an independent risk factor and among those with cardiovascular comorbidities. A large body of evidence suggests a causal link between serum phosphorus concentration and mortality in CKD. The following studies provide evidence that phosphorus retention is associated with increased risk of mortality.
### Table 1-4  Serum Phosphorus Levels and Mortality

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Voormolen, Noordzij, 2007, Nephrol Dial Transplant) (PREPARE)</td>
<td>CKD pre-dialysis (eGFR 13 mL/min/1.73m²)</td>
<td>547</td>
<td>High serum phosphorus is an independent risk factor for death. Mortality risk was 25% per mg/dL in serum phosphorus which increased to 62% after adjustment.</td>
</tr>
<tr>
<td>(Tonelli, Sacks, 2005, Circulation) (CARE)</td>
<td>Non-CKD Prior coronary disease</td>
<td>4,127</td>
<td>Significant, graded, independent relation between higher serum phosphorus and the risk of death. Phosphorus ≥4 mg/dL had a significantly 32% increase risk for all-cause mortality when compared to phosphorus levels between 2.5 and 3.4 mg/dL. The group with baseline values ≥3.5 mg/dL had a significantly 27% increase risk for all-cause mortality when compared to phosphorus levels &lt; 3.5 mg/dL.</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, J Am Soc Nephrol)</td>
<td>CKD pre-dialysis</td>
<td>6,730</td>
<td>After a median follow-up of 2.1 years, 32.5% had died, 7.4% reached ESRD and 4.5% were lost to follow-up. It was estimated that for each 1 mg/dL (0.323 mmol/L) increase in serum phosphorus, there was a 23% increased risk of death. There was a statistically significant increase in mortality risk associated with phosphorus levels &gt; 3.5 mg/dL.</td>
</tr>
</tbody>
</table>

There is a large body of epidemiological evidence linking the common disturbances of bone and mineral metabolism with increased risk of death in CKD patients, primarily due to increased atherosclerotic burden and cardiovascular events. Across a number of additional studies, the documented threshold of serum phosphorus concentration for a significant increased risk ranges from 3.5 to >6.5 mg/dL, and when analyzed as a continuous variable a 1 mg/dL increment in the serum phosphorus concentration is associated with a 4% to 9% higher mortality risk. It is estimated that correction of hyperphosphatemia could save nearly 34,000 patient life years in the US over a 5-year period (Port, Pisoni, 2004, Blood Purif; Young, 2007, Adv Chronic Kidney Dis). The association between serum phosphorus and mortality does not necessarily prove a causal relationship. Mortality could be related to other factors such as comorbidity or non-compliance. However, three factors suggest a causal relationship: (1) the results have been replicated in several large studies using different populations and study designs; (2) each of those studies used multivariate-regression techniques to adjust for many potential confounding variables; and (3) the epidemiologic data
are consistent with other observational and experimental data suggesting plausible biologic mechanisms. Therefore, a causal link between serum phosphorus concentration and mortality of CKD seems likely.

Current Treatment

Hyperphosphatemia manifests prior to CKD Stage 5 and the need for renal replacement therapy. To that end, the NKF recommends treatment of hyperphosphatemia prior to the initiation of dialysis; current KDOQI guidelines recommend that monitoring for disordered mineral metabolism begin in patients with CKD Stage 3, and that serum phosphorus be maintained within the target range of 2.7 to 4.6 mg/dL in patients with CKD Stages 3 and 4 or 3.5 to 5.5 mg/dL for CKD Stage 5 (NKF, 2003, Am J Kidney Dis) through dietary phosphate restriction, dialysis, and the use of phosphate binders. This updated public health approach to treatment of CKD, involving identification of patients with early kidney disease and more aggressive treatment strategies, aims to reduce the clinical consequences of hyperphosphatemia and may decrease or delay cardiovascular morbidity and mortality.

Evaluation of Benefits and Risks of Phosphate Binder Therapy for Hyperphosphatemia in Patients with CKD Not on Dialysis Therapy

Abnormalities in phosphate metabolism develop early in CKD and become manifest once GFR decreases below 30 mL/min. The goal of treatment for CKD is to prevent emergence of the disorders comprising CKD-MBD including renal osteodystrophy, extraskeletal calcifications, and CVD. The prevention of extraskeletal calcifications and cardiovascular complications of uremia will be an important step in attempting to improve patient survival.

It is anticipated that the benefits of early initiation of phosphate binder therapy when hyperphosphatemia begins, in conjunction with improved assessment of bone turnover, PTH levels and active vitamin D therapy will yield improvements in bone health and overall health. The benefits of control of hyperphosphatemia include prevention of calciphylaxis and vascular calcification as these have been associated with high plasma phosphate levels. The prevention of complications related to CKD-MBD in association with active vitamin D or vitamin D supplements is also important for maintaining bone health in these patients. It is predicted that the benefits of controlling biochemical parameters related to CKD-MBD will translate into improvements in morbidity and mortality from CVD in this patient population.

The overall risks of phosphate binder therapy prior to initiation of dialysis are very small. The most frequent risk is related to mild and transient GI disturbances that are common to all
phosphate binders (i.e. nausea, vomiting, diarrhea and constipation). Hypophosphatemia as a consequence of binder use is rare, and is usually a result of inadequate nutrition and associated low phosphate intake. Drug-drug interactions are few, are usually of the type associated with adsorption to the binder, and are the same as for over-the-counter antacids. The above risks are easily mitigated and should not contribute to safety issues if patients receive regular physician care. Current phosphate binders share characteristics of antacids and ion exchange resins, which have been approved for use since the 1970s and have not been associated with significant risks. All three marketed phosphate binders have been extensively studied in the CKD population on dialysis and product specific risks are presented in the individual labeling for the three products (PhosLo, Renagel, and Fosrenol, see Sections 9.1, 9.2, and 9.3). The overall risks of phosphate binder therapy for patients with CKD not on dialysis are believed to be the same as or less than for patients on dialysis.

**Conclusion**

In accordance with the recognized contribution of hyperphosphatemia to cardiovascular morbidity and mortality, and the benefits of early detection and treatment of hyperphosphatemia, all three companies believe that there is sufficient evidence to support expanding the current indication for phosphate binders to control of hyperphosphatemia in CKD patients prior to and following the initiation of dialysis.
2. BACKGROUND OF CKD

2.1 Overview

CKD is a progressive disease in which over time the filtering capacity of the kidney gradually diminishes until renal replacement therapy is required. CKD is a major public health problem associated with significant morbidity, mortality and economic costs. CKD at early stages of renal dysfunction has been estimated to affect 10% of the adult US population, and as many as 400,000 patients currently are receiving some form of renal replacement therapy (Coresh, Astor, 2003, *Am J Kidney Dis*; Kinney, 2006, *Am J Kidney Dis*; Szczech and Lazar, 2004, *Kidney Int Suppl*; USRDS, 2006).

The Kidney Disease Improving Global Outcomes (KDIGO) group recently defined CKD-Mineral and Bone Disorder (CKD-MBD) in recognition that CKD is associated with a variety of complex metabolic and bone abnormalities (Moe, Drueke, 2006, *Kidney Int*). Considerable evidence now exists implicating a causal role of hyperphosphatemia and secondary hyperparathyroidism in CKD-MBD and its relation to increased morbidity and mortality in patients with CKD. Indeed, hyperphosphatemia is increasingly recognized as an independent risk factor for cardiovascular disease (CVD) and cardiovascular mortality in CKD patients.

CKD is classified (Stages 1-5) on the basis of the presence of kidney damage and the glomerular filtration rate (GFR). Hyperphosphatemia manifests prior to CKD Stage 5 and the need for renal replacement therapy. Thus, there is an opportunity via phosphate binder therapy to provide therapeutic benefit to CKD patients prior to dialysis. To that end, the National Kidney Foundation (NKF) recommends the treatment of hyperphosphatemia prior to the initiation of dialysis. Current KDOQI guidelines recommend that monitoring for disordered mineral metabolism begin in patients with CKD Stage 3, and that serum phosphorus be maintained within the target range of 2.7 to 4.6 mg/dL in patients with CKD Stages 3 and 4 or 3.5 to 5.5 mg/dL for CKD Stage 5 (NKF, 2003, *Am J Kidney Dis*). This updated public health approach to treatment of CKD, involving identification of patients with early kidney disease and more aggressive treatment strategies, aims to to reduce the clinical consequences of hyperphosphatemia and may decrease or delay cardiovascular morbidity and mortality. As currently indicated, approved treatments for control of phosphorus levels are delayed until dialysis has already begun, which, by definition, precludes attainment of these public health goals.
2.2 Definition of CKD

In 2000, the NKF Kidney Disease Outcome Quality Initiative (KDOQI) Advisory Board approved development of clinical practice guidelines to define CKD, to classify stages in the progression of CKD, and to treat CKD (NKF, 2002, *Am J Kidney Dis*).

CKD is defined as either kidney damage or a GFR of <60 mL/min/1.73m² for ≥3 months. Kidney damage itself is defined as the presence of pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (NKF, 2002, *Am J Kidney Dis*).

The GFR is accepted as the best measure of overall kidney function in health and disease (NKF, 2007, *Am J Kidney Dis*). CKD is defined on the basis of these criteria regardless of the type of kidney disease (underlying diagnosis).

2.3 Classification of CKD Stages 1-5

CKD is a spectrum of disease, with mild renal impairment at one end and established end-stage renal disease (ESRD) requiring renal replacement therapy at the other. The level of kidney function tends to decline over time in most patients with CKD. Consequently, CKD progresses as a continuum. CKD is classified by stages, as summarized in Table 2-1. (NKF, 2002, *Am J Kidney Dis*) Although convenient for diagnostic purposes, the apparently discrete divisions between these various CKD stages potentially mask the very nature of the disease as a continuum, with more subtle clinical distinctions between pre-dialysis and dialysis states and evidence for advantages of certain therapeutic interventions prior to the need for dialysis.
Table 2-1   Classification of CKD Stages 1-5 with Prevalence Data

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
<th>Prevalence in 2005 N (1000s)</th>
<th>Projected Prevalence in 2010 N (1000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage Normal or increased GFR</td>
<td>≥90</td>
<td>5,900</td>
<td>10,137</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage Mild decreased GFR</td>
<td>60 – 89</td>
<td>5,300</td>
<td>9,067</td>
</tr>
<tr>
<td>3</td>
<td>Moderate or decreased GFR</td>
<td>30 – 59</td>
<td>8,202</td>
<td>11,506</td>
</tr>
<tr>
<td>4</td>
<td>Severe decreased GFR</td>
<td>15 – 29</td>
<td>442</td>
<td>620</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
<td>367</td>
<td>565</td>
</tr>
</tbody>
</table>


2.4   CKD as a Global Health Issue

CKD is a worldwide public health problem, estimated to affect 11% of the global population and 10% of the US population (Coresh, Byrd-Holt, 2005, *J Am Soc Nephrol*; Mitra, Tasker, 2007, *Bmj*; Stevens, Coresh, 2006, *N Engl J Med*). This percentage significantly rises in those over 70 years of age (Mitra, Tasker, 2007, *Bmj*). The prevalence of CKD is rising both as a consequence of an aging population and as a result of an increase in causative conditions such as obesity, hypertension, and diabetes, which account for a US prevalence of 127 million adults, 50 million adults, and 18 million adults, respectively (NKF, 2004, *Am J Kidney Dis*).

Using the definition of CKD Stages 1-5 described above, the prevalence of individuals with CKD at earlier stages of renal dysfunction has been estimated at 10% of the adult US population, and more than 400,000 patients currently are receiving some form of renal replacement therapy. Using serum creatinine as a marker of disease progression, analysis of the NHANES III dataset indicates substantial numbers of patients at all phases of CKD and estimates that the number of patients with serum creatinine >2.0 mg/dL is greater than 800,000 (Hsu and Chertow, 2002, *Nephrol Dial Transplant*).

Despite many medical advances, the mortality rate for patients with CKD receiving dialysis is in excess of 20% per year (Foley, Parfrey, 1998, *Am J Kidney Dis*). Cardiovascular disease remains the leading cause of death in the dialysis population, with almost half of all deaths on dialysis due to cardiovascular events (Collins, Li, 2001, *Am J Kidney Dis*; Herzog, 1999, *Kidney Int Suppl*; Herzog, 2002, *Nephrol Dial Transplant*). Mortality due to cardiovascular disease is 10 to 20 times greater in hemodialysis patients compared to the


2.5 Treatment Guidelines

In recognition of the complex nature of CKD as it relates to both causal co-morbidities and adverse outcomes, the KDOQI Working Group has issued a number of guidelines for treatment of CKD. The guidelines with particular relevance to the discussion presented in this briefing package are referenced as appropriate in additional sections of this document.
3. MINERAL BALANCE PHYSIOLOGY AND PATHOPHYSIOLOGY

3.1 Introduction

The capacity to regulate phosphorus and calcium metabolism becomes compromised progressively as kidney function declines (Goodman, 2003, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism). This is due in large part because the kidneys serve to maintain total body phosphorus and calcium balance by modulating the amounts of each mineral that are excreted daily in the urine. This section reviews mechanisms that maintain phosphorus balance and the pathophysiology of CKD.

3.2 Normal Phosphorus Metabolism

3.2.1 Phosphorus Balance

In healthy adults, the total body content of phosphorus is approximately 700 g (Yu, 2004), and the normal plasma or serum phosphate concentration is 3.81 ± 1.15 mg/dL (1.23 ± 0.37 mmol/L) (Nordin, 1976, Calcium, Phosphate and Magnesium Metabolism (Clinical Physiology and Diagnostic Procedures)). As shown in Figure 3-1, phosphorus is distributed primarily (85%) in mineralized skeletal tissue, where it is in the form of hydroxyapatite (Yu, 2004). Approximately 15% of phosphorus is located in soft tissues, particularly in muscle. Less than 1% of phosphorus is found in extracellular fluid (mostly plasma and serum), primarily as monovalent phosphate (H2PO4\(^-\)) and divalent phosphate (HPO4\(^{2-}\)), in a ratio of 4:1 at pH 7.4. Plasma phosphorus concentrations are measured and reported as mg or mmol of inorganic phosphorus.

In healthy adults, net skeletal phosphorus balance is neutral, or close to zero. As depicted in Figure 3-1, extracellular fluid (i.e., plasma and serum) phosphorus concentration is a function of intestinal absorption, ongoing skeletal remodeling, and exchange with soft tissues. Daily dietary intake of phosphorus in adults (principally from dietary protein, dairy products, and food additives) typically ranges from 1000 mg/day to 1200 mg/day. The gastrointestinal tract absorbs 60 to 70% of this amount, or 600 mg/day to 800 mg/day. Ongoing skeletal remodeling contributes approximately 120 mg to 150 mg phosphorus daily to extracellular fluid. To maintain neutral phosphorus balance, the kidneys must excrete the 600 mg to 800 mg of phosphorus absorbed from the gastrointestinal tract plus any phosphorus not reabsorbed by bone. Under steady-state conditions in healthy adults, skeletal remodeling is relatively close to being in balance. Thus, any contribution of bone metabolism to extracellular phosphorus concentration is negligible, and the amount of phosphorus excreted by the kidneys to maintain neutral phosphorus balance principally reflects net intestinal
phosphorus absorption. Due to the large inherent capacity of the kidney to modify phosphorus excretion, variations in the rate of skeletal remodeling and in the amount of phosphorus exchanged daily between bone and the extracellular fluid do not usually affect serum phosphorus levels until renal function is significantly impaired (Goodman, 2005, *Med Clin North Am*).

**Figure 3-1** Distribution of Phosphorus Among Bone, Soft Tissues and Extracellular Fluid

3.2.2 **Phosphate Absorption / Elimination**

Intestinal phosphorus absorption (Figure 3-1) is composed of a passive, or diffusional, process that occurs primarily through the paracellular pathway. Additionally, an active process accounts for up to 1/3 of net phosphate absorption. This is mediated by a sodium-phosphate cotransporter located at the apical brush-border membrane of intestinal epithelial cells. This process is actively regulated by 1,25-(OH)$_2$ vitamin D (calcitriol) (Yanagawa, 1994, *Maxwell's and Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism*).

A normal plasma phosphorus level is maintained predominantly through renal clearance. Most inorganic phosphorus in plasma is in an ultrafilterable form. It readily crosses the filtration barrier within the glomerulus and is found in proximal tubular fluid at concentrations similar to those in plasma. Approximately 70 to 80% of the filtered load of phosphorus is reabsorbed in the proximal nephron, which serves as the primary site for regulating phosphorus excretion in the urine. This reabsorption is mediated primarily by the type 2 sodium-phosphorus cotransporter (Npt2a) in the cells of the proximal tubule. Smaller amounts of phosphorus are reabsorbed in more distal nephron segments. Thus, the proximal tubule is the primary site for regulating phosphorus excretion in the urine.
3.3 Regulation of Phosphorus Homeostasis

3.3.1 Hormonal Systems

There are at least two hormonal systems that control phosphorus (Figure 3-2). One system, which helps to increase phosphorus (positive-phosphate hormone system), is mediated in part by calcitriol, which helps promote phosphorus absorption across the gastrointestinal tract acting through the Na-phosphate cotransporter Npt2b in the intestinal epithelial cells (Yanagawa, 1994, Maxwell's and Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism). Parathyroid hormone (PTH) is a potent modifier of renal phosphorus excretion and increases renal phosphorus excretion by blocking phosphorus reabsorption in the proximal tubule through its action on Npt2a and concomitantly increases $1\alpha$-hydroxylation of calcitriol, thus raising calcitriol levels (Kempson, Lotscher, 1995, Am J Physiol).

The second system which helps to decrease phosphorus (negative-phosphate hormone system) is mediated by the phosphatonin, fibroblast growth factor 23 (FGF-23). FGF-23 is a key determinant of phosphorus transport within the nephron and increases phosphorus excretion by decreasing phosphorus reabsorption in the proximal tubule through Npt2a similar to PTH. However, FGF-23 blocks $1\alpha$-hydroxylation of calcitriol, thus lowering calcitriol levels, and lowering intestinal absorption of phosphorus (Fukagawa and Kazama, 2006, Pediatr Nephrol). Additionally, FGF-23 may regulate phosphorus uptake into the bone by osteoblasts and mediate skeletal mineralization. FGF-23 is produced in skeletal osteoblasts and osteocytes, and its production is stimulated by elevated phosphate and elevated calcitriol (Fukagawa and Kazama, 2006, Pediatr Nephrol).
3.3.2 **Altered Phosphorus Balance in CKD**

Since the kidney plays a pivotal role in modulating phosphorus balance, as kidney function declines, phosphorus homeostasis is disrupted. Positive phosphorus balance and hyperphosphatemia are hallmarks of advanced CKD. High plasma phosphorus levels inhibit renal 1α-hydroxylase activity. Calcitriol levels are decreased due to deficient 1α-hydroxylation (Portale, Booth, 1982, *Kidney Int*) with consequently lower intestinal calcium absorption, hypocalcemia, and stimulation of PTH production. A decrease in the amount of filtered phosphorus with declining kidney function leads to hyperphosphatemia, hypocalcemia, and stimulation of PTH and FGF-23 production (NKF, 2003, *Am J Kidney Dis*). The higher PTH and FGF-23 levels enhance urinary clearance of phosphorus by lowering proximal tubular reabsorption, thus ensuring “normal” plasma phosphorus levels, but at the expense of secondary hyperparathyroidism. Eventually, despite low rates of tubular reabsorption, phosphorus excretion declines and hyperphosphatemia is fixed.

3.4 **Pathophysiology of Hyperphosphatemia**

The major underlying cause of hyperphosphatemia is impaired renal phosphorus excretion. Although the capacity to increase phosphorus excretion is quite large in persons with normal renal function, urinary excretion of phosphorus becomes inadequate to accommodate the
amounts absorbed daily from the gastrointestinal tract when GFRs significantly decline, as shown in Figure 3-3 (Slatopolsky, Robson, 1968, *J Clin Invest*).

**Figure 3-3**  
Comparison of Tubular Reabsorption of Phosphorus (TRP) with GFRs for 24 Patients with Chronic Progressive Bilateral Renal Disease and six Healthy Individuals

As seen in the illustrative example in Figure 3-4, CKD is accompanied by an inability to excrete the amount of phosphorus absorbed daily (16 mg/kg/day absorbed and only 12 mg/kg/day excreted). The positive phosphorus balance is reflected in the exchangeable phosphorus pool including the blood because exit from the pool by way of excretion by the kidney or deposition in the bone storage pool is limited.
Basically, hyperphosphatemia is excretion failure. Unfortunately, the additional phosphorus cannot be stored in the bone because the skeleton in kidney failure is in a permanent state of imbalance favoring resorption. There are two general types of skeletal remodeling disorder in CKD: low turnover or high turnover disorders. In low bone turnover disease, bone cannot incorporate excess phosphorus. Consequently, the excess phosphorus is deposited into heterotopic sites, such as renal and cardiovascular sites. In high bone turnover bone disease, despite increased movement of phosphorus into the depot, the rates of phosphorus exit are still greater. Excessive resorption of bone releases phosphorus and calcium into the circulation, aggravating hyperphosphatemia and causing hypercalcemia. As a result, one can see that hyperphosphatemia represents a breakdown in phosphorus homeostasis (Hruska, Saab, 2007, Semin Dial) that creates a state of positive phosphorus balance in the body.

3.4.1 Hyperphosphatemia is a Late Complication of CKD

During CKD progression, most patients who are well-nourished are in positive phosphorus balance. Sometimes in CKD Stage 3 and often in CKD Stages 4 and 5, significant positive phosphorus balance will occur as the kidney fails to excrete the absorbed phosphate load (Figure 3-5).

A cross-sectional analysis of baseline data from an observational study evaluated the relationships of circulating vitamin D, PTH, calcium and phosphorus in CKD patients who were not receiving dialysis (Levin, Bakris, 2007, Kidney Int). As shown in Figure 3-5 (Levin, Bakris, 2007, Kidney Int), there is an increase in the prevalence of abnormal PTH across declining eGFR levels. The levels of serum calcium and phosphorus remain relatively stable until eGFR decreases to <20 mL/min/1.73 m² whereas abnormal PTH begins to occur
at levels of 45 mL/min/1.73 m². These data indicate that elevated levels of phosphorus and calcium are poor markers of elevated PTH. Phosphorus and calcium levels fail to increase proportionally with the rise in PTH and only rise above their normal ranges in the late stages of CKD. Therefore, frank hyperphosphatemia is a late complication of CKD.

**Figure 3-5** Prevalence of Abnormal Serum Calcium, Phosphorus, and Intact PTH by GFR

In another cross sectional study (Craver, Marco, 2007, *Nephrol Dial Transplant*), mineral metabolism as a function of CKD in 1,836 patients with different stages of CKD show that a decrease in calcitriol, a decrease in total urinary phosphorus excretion, and an increase in PTH are the earliest mineral metabolism alterations in CKD, while serum calcium and phosphate are altered later in the course of CKD. Figure 3-5 shows the mean values of calcium, phosphorus, PTH, and calcitriol. PTH starts to increase at CKD Stage 2 and rises progressively and significantly until CKD Stage 5. Calcitriol decreases at CKD Stage 2 and decreases progressively as CKD advances.

Serum calcium levels increase from CKD Stages 1 to 2 and decrease afterwards. Serum phosphorus shows a mirror image with respect to calcium levels.
Figure 3-6  Mineral Metabolism as a Function of CKD

Figure 3-6 also shows the subgroup of patients with data from 24-hour urine collection. Urine phosphorus and calcium excretion decreases as renal function deteriorates. Fractional excretion of phosphorus increases gradually and significantly from CKD Stages 1 to 4; significance was not obtained between CKD Stages 4 and 5 due to saturation of the capacity of remaining nephrons to excrete phosphorus.
To summarize, mineral metabolism disturbances start early in the course of CKD. The first alterations to take place are increased fractional excretion of phosphate, increased serum parathyroid hormone levels, decreased serum calcitriol levels, and decreased 24-h urine phosphate, which show significant level variation when the GFR falls below 60 mL/min/1.73m².

3.5 Conclusion

Fractional excretion of phosphorus increases gradually and significantly from CKD Stages 1 to 5 to maintain balance. Sometimes in CKD Stage 3 and often in CKD Stages 4 and 5, significant positive phosphorus balance will occur as the kidney fails to excrete the absorbed phosphate load. Therefore, hyperphosphatemia is a hallmark of advanced CKD. The pathophysiological consequence of hyperphosphatemia is bone turnover disease. With low bone turnover bone disease, excess phosphorus goes into heterotopic sites, such as the kidney and cardiovascular systems. With high bone turnover bone disease excessive resorption of bone releases phosphorus and calcium into the circulation, aggravating hyperphosphatemia and causing hypercalcemia. Hyperphosphatemia, vitamin D deficiency, and secondary hyperparathyroidism are predictable consequences of the progressive decline in GFR among patients with CKD.
4. CLINICAL CONSEQUENCES OF HYPERPHOSPHATEMIA

4.1 Introduction

Hyperphosphatemia directly stimulates PTH secretion and parathyroid cell proliferation, both in vitro and in vivo. Hyperphosphatemia also reduces blood levels of calcium, which in turn stimulates PTH secretion. High PTH reduces tubular reabsorption of phosphorus and returns serum phosphorus toward normal. Thus, “normal” serum phosphorus levels seen in early stages of CKD are only at the expense of elevated circulating PTH levels. A high level of PTH increases bone turnover, enhances bone resorption, and releases calcium and phosphorus into the circulation, causing hypercalcemia and aggravating hyperphosphatemia (Slatopolsky, Finch, 1996, J Clin Invest). Excess phosphate results in inhibition of the activity of the renal enzyme 1α-hydroxylase, which converts vitamin D to active calcitriol, contributing to vitamin D deficiency in CKD. In CKD, high PTH, high phosphorus, low calcium levels, and vitamin D deficiency are all part of the disturbed mineral metabolism that is a common complication of these patients.

4.2 Consequences of Hyperphosphatemia

4.2.1 Phosphorus Imbalance

One of the earliest manifestations of CKD is the failure to regulate phosphorus balance, which occurs as part of the systemic disorder of mineral and bone metabolism associated with CKD. Reduced GFR and reduced secretion of active vitamin D result in the accumulation of abnormal concentrations of phosphorus and calcium. The renal-parathyroid axis responds to these abnormal concentrations through surprisingly adaptive mechanisms, often maintaining “normal” serum phosphorus levels until the very late stages of renal disease despite a significantly compromised GFR. By the time hyperphosphatemia presents, parathyroid hyperplasia is present, and bone loss and soft tissue calcification are often present (McCarron, 2005, J Am Soc Nephrol).

As the GFR falls, hyperphosphatemia and hypocalcemia (secondary to vitamin D deficiency) develop and act as stimuli for parathyroid hormone (PTH) secretion. Parathyroid hormone stimulates bone osteoclasts to resorb bone, liberating calcium and phosphate, thus readjusting serum calcium to near normal. In addition, PTH promotes the excretion of phosphorus by decreasing its reabsorption in residual nephrons. However, once GFR falls to less than 25% of normal, the elevation of PTH cannot further increase phosphorus excretion, and serum phosphorus concentration starts to increase (Delmez and Slatopolsky, 1992, Am J Kidney Dis; Slatopolsky and Bricker, 1973, Kidney Int). Figure 4-1 shows the serum phosphorus...
levels plotted against GFR in over 3,400 patients in a retrospective analysis (Kestenbaum, Sampson, 2005, *J Am Soc Nephrol*). This study suggests that demonstrable phosphorus increments begin to occur when GFR levels fall below 30 mL/min/1.73m².

**Figure 4-1 Mean Serum Phosphorus Levels as a Function of Baseline GFR**

![Figure 4-1](image)

Using the NHANES III database, Hsu and Chertow found hyperphosphatemia was present in 3, 7, and 30% of patients with GFRs between 40 to 30; 30 to 20; and < 20 mL/min/1.73m², respectively (Hsu and Chertow, 2002, *Nephrol Dial Transplant*).

### 4.2.2 Secondary Hyperparathyroidism

Excess phosphorus is a driving force behind secondary hyperparathyroidism. Hyperphosphatemia and hyperparathyroidism are part of a self-reinforcing feedback loop with serious consequences (Figure 4-2). The associated high turnover bone disease manifests with bone pain, bone fracture, bone deformity, osteopenia, myopathy, arthritis, resistance to erythropoietin due to marrow fibrosis, growth failure in children, and extraskeletal calcification. These are important causes of morbidity, decreased quality of life, and mortality (Levin, 2003, *Semin Dial*; Moe, Drueke, 2006, *Kidney Int*).

As renal function declines, calcitriol production by the kidney is impaired, in addition to hyperphosphatemia. This results in secondary hyperparathyroidism, associated with hyperplasia and hypertrophy of the parathyroid glands, the cells of which become more resistant to suppression by vitamin D (Leavey and Weitzel, 2002, *Endocrinol Metab Clin*).
Higher doses of vitamin D analogues may be required to suppress PTH synthesis (Leavey and Weitzel, 2002, *Endocrinol Metab Clin North Am*). Increases in PTH, plus the abnormalities in phosphorus and calcium balance, lead to disturbances of bone metabolism. In a study in 1,814 ambulatory CKD patients (Levin, Bakris, 2007, *Kidney Int*), 71% of whom were from primary care practices, low serum calcitriol levels (<22 pg/mL) were seen in more than 60% of patients whose GFR was <30 mL/min/1.73m². Low calcitriol levels and elevated PTH levels were commonly seen at higher GFR levels than previously reported.

About 30 to 40% of bone biopsies in CKD Stage 5 patients not receiving phosphate binder treatment show PTH-dependent high bone turnover coexisting with impaired mineralization (i.e., mixed uremic osteodystrophy). Another 30% show predominantly high bone turnover lesions (i.e., osteitis fibrosa). A further 30% show low bone turnover, in which bone absorption and turnover appear blunted histomorphologically (Leavey and Weitzel, 2002, *Endocrinol Metab Clin North Am*). Both high turnover and adynamic (low turnover) bone disease exacerbate hyperphosphatemia.

Secondary hyperparathyroidism is itself associated with myocardial infarction (odds ratio 1.6) and congestive heart failure (CHF) (odds ratio 2.0), as well as acidosis (De Boer, Gorodetskaya, 2002, *J Am Soc Nephrol*).

**Figure 4-2  Secondary Hyperparathyroidism**

---

*Note: Diagram shows the interactions between PTH, calcium, phosphorus, and vitamin D, as well as the systemic toxicity and bone disease outcomes.*
4.2.3 Bone Disease


Nearly all CKD Stage 5 patients requiring dialysis have some degree of abnormal bone histology, and a spectrum of histological abnormality of bone may be observed (high-turnover hyperparathyroid bone disease; low-turnover bone disease, i.e., adynamic bone disease and osteomalacia). Dialysis patients suffer an increased incidence of hip fractures. Based on the USRDS, the relative risk (RR) for hip fracture was elevated in both male (RR 4.44) and female (RR 4.0) CKD Stage 5 patients compared with the general population (Kestenbaum and Belozeroff, 2007, Eur J Clin Invest). Factors associated with increased fracture risk were similar to those in the general population, including age, body mass index (BMI), and the presence of peripheral vascular disease (PVD), i.e. no independent renal factor was found to be related to hip fracture risk (Kestenbaum and Belozeroff, 2007, Eur J Clin Invest). In contrast to these findings, multivariate analysis indicated that duration of dialysis is a putative risk factor for hip fracture (Moe, Drueke, 2007, Adv Chronic Kidney Dis). In this study, Moe et al. reported that dialysis patients in their fourth decade of life have a relative risk of hip fracture that is 80-fold higher than that of age-matched and sex-matched control subjects, and hip fracture in dialysis patients is associated with a doubling of the mortality observed in hip fractures in non-dialysis patients (Moe, Drueke, 2007, Adv Chronic Kidney Dis).

4.2.3.1 Renal Osteodystrophy

Renal osteodystrophy is an alteration of bone morphology in CKD and is a measure of the skeletal component of the systemic disorder of CKD-MBD that is quantitative by histomorphometry of bone biopsy. It is a common complication of CKD Stages 3 through 5 and one of the most important non-traditional risk factors associated with CVD in CKD (Lee, Benner, 2007, J Ren Nutr). Phosphorus retention plays an important role in the pathogenesis of hyperparathyroidism (Locatelli, Cannata-Andia, 2002, Nephrol Dial Transplant).
Although hyperphosphatemia is often absent in CKD Stage 3 (see above), elevated PTH levels are more common (Richards, 2006, *XLIII ERA-EDTA Congress*). Richards et al. reported an abnormally elevated PTH in 20% of patients with CKD Stage 3 (Richards, 2006, *XLIII ERA-EDTA Congress*), and the NKF Kidney Early Evaluation Program (NKF-KEEP) reported approximately 25 and 75% for CKD Stage 3 and CKD Stage 4 patients, respectively (NKF, 2007, *Am J Kidney Dis*). A positive association between high serum PTH and increased death risk has been established among patients on maintenance hemodialysis (Kalantar-Zadeh, Kuwae, 2006, *Kidney Int*).

### 4.2.4 Vascular Calcification and Ectopic Calcification

In CKD, evidence suggests that serum levels of phosphorus and calcium appear to have a particularly important role in the pathogenesis of vascular calcification, which leads to atherosclerosis and cardiovascular events. Exposure of human vascular smooth muscle cells *in vitro* to elevated levels of inorganic phosphorus or extracellular calcium both stimulate increases in mineral deposition (Nishizawa, Jono, 2005, *J Ren Nutr*; Reynolds, Joannides, 2004, *J Am Soc Nephrol*; Yang, Curinga, 2004, *Kidney Int*). Furthermore, incubation of the cells in the presence of elevated phosphorus and calcium has proven that the effects of these minerals in promoting calcification are synergistic (Reynolds, Joannides, 2004, *J Am Soc Nephrol*).

Investigations have also provided some potential mechanistic links between elevated serum phosphorus and vascular calcification (Figure 4-3). The presence of phosphonoformic acid, an antagonist of the sodium-dependent phosphate cotransporter (Pit-1), has been shown to inhibit mineralization of vascular smooth muscle cells induced by elevated levels of phosphorus or calcium (Nishizawa, Jono, 2005, *J Ren Nutr*; Yang, Curinga, 2004, *Kidney Int*). This indicates that vascular calcification may be dependent on active cellular uptake of phosphorus. It is thought that elevated phosphorus stimulates phosphorus uptake via Pit-1, whereas increased calcium induces expression of Pit 1 mRNA (Giachelli, 2004, *J Am Soc Nephrol*). Exposure of human smooth muscle cells to elevated levels of phosphorus upregulates expression of the osteoblastic differentiation markers osteocalcin and core binding factor α-1 (Cbfa-1) (Nishizawa, Jono, 2005, *J Ren Nutr*). Whether expression of Cbfa-1 is critical for the differentiation or is merely a marker remains unknown. *In vivo*, hyperphosphatemia has been shown to promote osterix expression (a transcription factor essential for osteoblast differentiation and bone formation) in the aorta of a rat model of CKD and type 2 diabetes (Mathew, 2006, *J Am Soc Nephrol*). Thus, it is thought that elevated intracellular phosphorus may directly stimulate smooth muscle cells to undergo
phenotypic changes that predispose to calcification, stimulating upregulation of various osteogenic genes (Giachelli, 2004, *J Am Soc Nephrol*). These bone-like cells may lay down a bone matrix type I collagen and noncollagenous material. Mineralization of this matrix may occur through a process guided by matrix proteins and osteoblast-like cells. The latter step is likely to be accelerated in the presence of high serum calcium and phosphate levels (Moe, 2004, *Semin Nephrol*).

A further mechanism by which elevated phosphorus and calcium may promote vascular calcification is via the stimulation of apoptotic vascular smooth muscle cell death and release of apoptotic bodies (matrix vesicles) (Figure 4-3). Apoptotic bodies released by vascular smooth muscle cells following *in vitro* exposure to calcium and phosphorus contain calcium phosphate apatite and may act as initiation sites for apatite crystallization (Reynolds, Joannides, 2004, *J Am Soc Nephrol*).
In addition to growing basic scientific evidence, there are some clinical findings that support the role of serum phosphorus and calcium in stimulating vascular calcification. A study of young patients on dialysis, for example, demonstrated that serum phosphorus concentrations tended to be higher (p = 0.06) and the calcium x phosphorus product in serum was significantly higher (p = 0.04) in patients with CAC than in those without calcification (Goodman, Goldin, 2000, *N Engl J Med*).

Although serum phosphorus is the main player in the link between disturbed mineral metabolism and vascular calcification, vitamin D, PTH, and calcium are also involved. Vitamin D receptors are found on vascular smooth muscle cells (Inoue and Kawashima, 1988, *Biochem Biophys Res Commun*), and high doses of calcitriol have been shown to induce mineralization of these cells *in vitro* (Jono, Nishizawa, 1998, *Circulation*).
Oversuppression of PTH may also contribute to progression of vascular calcification in patients with CKD. It has been demonstrated that human PTH (1–34) inhibits calcification and aortic osteogenic differentiation in a murine model of arterial calcification (Shao, Cheng, 2003, *J Biol Chem*). In addition, vascular smooth muscle cells demonstrate reduced mineralization in the presence of a PTH-related peptide *in vitro* (Jono, Nishizawa, 1997, *Arterioscler Thromb Vasc Biol*). In dialysis patients, an inverse relationship between PTH and calcification exists (Guerin, London, 2000, *Nephrol Dial Transplant*). Thus, appropriate physiological levels of PTH may be protective; oversuppression of PTH may contribute to adynamic bone disease (D’Haese, Spasovski, 2003, *Kidney Int Suppl*) and may increase calcification risk. It is worth noting that patients with CKD with adynamic bone disease with both low PTH and increased phosphorus and calcium, could be subject to a particularly high risk of vascular calcification as the lack of bone turnover limits the capacity of bone to store excess phosphorus and calcium.

Nonetheless, vascular calcification clearly occurs at earlier stages of CKD, when calcium is often normal and phosphorus levels are not often very high. However, it should be noted that serum phosphorus levels are not a good marker of total phosphorus load in early stages of CKD, as increased PTH levels act to control serum phosphorus. To put the clinical findings in context with the emerging data from cell culture and animal studies, it is reasonable to conclude that positive phosphorus balance and hyperphosphatemia contribute to the progression of vascular calcification that begins in early stages of CKD, is accelerated in CKD Stage 5, and is established in many patients at the time of initiation of maintenance dialysis therapy. The presence of vascular calcification, as measured by electron-beam computed tomography, confirms the presence of atherosclerotic plaques (Shulman, Ford, 1989, *Hypertension*) and lesions with stenosis (NKF, 2002, *Am J Kidney Dis*). Thus, disordered mineral metabolism with vascular calcification contributes to the progression of atherosclerosis and cardiovascular events in CKD patients (Mehrotra, 2006, *J Ren Nutr*; Mehrotra, Budoff, 2005, *Kidney Int*).

phenotype having high serum phosphorus levels, vascular calcification, atherosclerosis, and premature aging (i.e., the Klotho null mouse). In the Klotho null mouse, the phenotype is reversible by treatment with a low-phosphorus diet (Morishita, Shirai, 2001, *J Nutr*).

Polymorphisms of this gene have been associated with increased risk of cardiovascular disease in patients with previous myocardial infarction and dyslipidemia but normal kidney function (Arking, Atzmon, 2005, *Circ Res*).

In conclusion, there is evidence that excess phosphorus plays a key role in the pathogenesis of vascular calcification in patients with CKD.

### 4.2.4.1 Pathogenesis of Vascular Calcification

Vascular calcification is remarkably more prevalent and severe in CKD and ESRD than the general population. It was initially thought to occur via passive precipitation of amorphous calcium phosphate matrix alone (Moe, Drueke, 2007, *Adv Chronic Kidney Dis*). Further investigation, however, has revealed it to be an active process in which vascular smooth muscle cells acquire an osteoblast-like phenotype (Johnson, Leopold, 2006, *Circ Res*). The mechanism underlying this process has been a top area of research interest in the nephrology community. It appears that the vascular calcification is a result of imbalance of the inducers and inhibitors in the system. Vascular calcification occurs by proliferation of inducers or downregulation of inhibitors. Phosphorus is recognized as one of the inducers. (Figure 4-4)
4.2.5 Soft Tissue Calcification and Effects on Other Organs

Uremic extraskeletal calcification affects arterial walls (vascular calcification); organs such as the heart, lungs, and kidneys (visceral calcification); and periarticular, cutaneous, and subcutaneous tissues. Elevated levels of PTH, tissue alkalinity, hyperphosphatemia, and, in particular, elevated calcium-phosphate (Ca x P) product all combine to increase tissue calcification (Parfitt, 1969, *Arch Intern Med*). Numerous studies have shown that uremia, hyperphosphatemia, and secondary hyperparathyroidism may also affect the function of a number of other organs and tissues besides the bone and kidney, including the brain, heart, smooth muscles, lungs, erythrocytes, lymphocytes, pancreas, adrenal glands, and testes (Bro and Olgaard, 1997, *Am J Kidney Dis*).

In addition to the role of phosphorus to actively regulate the calcification process in vascular walls, phosphorus also plays a direct role in extraskeletal calcification. The positive phosphorus balance due to CKD results in deposition of calcium-phosphate complexes in tissues and organs throughout the body, particularly in the state of low turnover bone disease (when bone cannot absorb excess phosphorus) and high turnover bone disease (when bone remodeling is overly active). The higher bone resorption releases phosphorus and calcium into tissues and circulation.
### 4.2.6 Phosphorus and Vascular Calcification in Clinical Trials

The following table (Table 4-1) lists a number of studies describing the association of hyperphosphatemia and vascular calcification in patients with CKD, which are described in more detail below.

#### Table 4-1 Serum Phosphorus Levels and Vascular Calcification

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Russo, Corrao, 2007, <em>Am J Nephrol</em>)</td>
<td>CKD Stages 3-5 pre-dialysis Normal renal function</td>
<td>113</td>
<td>Coronary artery calcification (CAC) progression was significantly prominent in 51% of CKD patients ($p&lt;0.0001$). Although no association was observed between the clinical and biochemical variables and the total rates of CAC progression, rates above 75th percentile were significantly correlated with higher serum phosphorus levels despite a majority of the patients having “normal” levels of phosphorus according to KDOQI ($p=0.015$).</td>
</tr>
<tr>
<td>(Tomiyama, Higa, 2006, <em>Nephrol Dial Transplant</em>)</td>
<td>CKD (CrCl 15-90 mL/min/1.73m$^2$)</td>
<td>96</td>
<td>Higher levels of serum phosphorus were correlated with the presence of severe CAC (CAC score &gt; 400 Agatson units). Severe CAC were significantly associated with higher levels of phosphorus but not iPTH.</td>
</tr>
<tr>
<td>(Sigrist, Bungay, 2006, <em>Nephrol Dial Transplant</em>)</td>
<td>CKD Stage 4 pre-dialysis and Dialysis</td>
<td>134</td>
<td>Arterial calcification had begun in almost 50% of patients prior to initiation of dialysis, but no relationship between serum phosphorus, corrected calcium, iPTH or phosphate binder type or dose and degree of calcification. A possible explanation for their findings is that their patients had good mineral control and were receiving phosphate binders.</td>
</tr>
<tr>
<td>(Dellegrottaglie, Saran, 2006, <em>Am J Cardiol</em>)</td>
<td>CKD Stages 3-5 pre-dialysis (eGFR &lt; 50 mL/min/1.73m$^2$)</td>
<td>106</td>
<td>Approximately 69% of patients exhibited some CAC. More than 37% had CAC scores above 75th percentile for age- and gender-matched subjects without CKD. Approximately 5% had CAC scores above 90th percentile.</td>
</tr>
<tr>
<td>(Russo, Palmiero, 2004, <em>Am J Kidney Dis</em>)</td>
<td>CKD Stages 2-5 pre-dialysis Normal renal function</td>
<td>140</td>
<td>Serum phosphorus levels were above KDOQI goals in patients with Stages 2-4 CKD and CAC was found to be already present in the early phases of CKD.</td>
</tr>
</tbody>
</table>
In 2006, Tomiyama et al. studied the impact of traditional and non-traditional risk factors on coronary calcification of CKD patients before dialysis (Tomiyama, Higa, 2006, *Nephrol Dial Transplant*). The report was based on a cross-sectional study of 96 patients with CrCl in the range of 15 to 90 mL/min/1.73m², none of whom were treated with calcium-based phosphate binders or vitamin D analogs. Higher levels of serum phosphorus were correlated with the presence of severe CAC (CAC score >400 Agatson units) despite the majority of patients having normal levels of phosphorus and none being treated with phosphate binders. No significant differences in the prevalence or severity of CAC scores were noted among the stages of CKD. A comparison between patients with CAC (CAC score >0) and without CAC (CAC score = 0) demonstrated that CAC were significantly associated with higher levels of iPTH, but not with phosphorus. A comparison between patients with severe CAC (CAC score >400 Agatson units) and without severe CAC (CAC score <400 AU) demonstrated that severe CAC were significantly associated with higher levels of phosphorus but not iPTH.

Similarly, in a study of 140 patients (85 with CKD Stages 2 through 5, and 55 with normal renal function), Russo et al. observed that that serum phosphorus levels were above KDOQI goals in the CKD group (Russo, Palmiero, 2004, *Am J Kidney Dis*). CAC was found to be already present in the early phases of CKD, with a prevalence greater in CKD patients than in controls, but lower than in dialysis patients. They failed to predict the appearance or progression of CAC with serum concentrations of calcium, phosphorus, iPTH, or inflammation markers.

In another multicenter, prospective, observational study of 106 CKD (Stages 3 through 5) patients to assess the prevalence of CAC and its relation to cardiovascular risk factors and renal function related parameters, Delleggrottaglie et al. demonstrated that the extent of cardiovascular calcium in patients with pre-dialysis CKD is related to some traditional risk factors for atherosclerosis (Delleggrottaglie, Saran, 2006, *Am J Cardiol*). Even though the extent of CAC in pre-dialysis CKD patients was not associated with indices of abnormal renal function or progression in renal dysfunction, higher serum phosphorus, iPTH, and diabetes status were significantly associated with decreasing renal function \(p = 0.035\). They also found that approximately 69% of CKD patients exhibited some CAC, with more than 37% having CAC scores above 75th percentile for age- and gender-matched subjects without CKD and about 15% having CAC scores above the 90% percentile.

Sigrist et al. studied 134 patients (46 CKD Stage 4, 60 hemodialysis and 28 peritoneal dialysis) in a cross-sectional study of matched CKD Stage 4 and 5 patients to assess the prevalence and severity of vascular calcification (Sigrist, Bungay, 2006, *Nephrol Dial* ...
Transplant). They found that the process of arterial calcification had begun in almost 50% of patients prior to initiation of dialysis, but no relationship between serum phosphorus, corrected calcium, iPTH, or phosphate binder type, or dose and degree of calcification. A possible explanation for their findings is that their patients had good mineral control and were receiving phosphate binders.

In a subsequent study, Russo et al. (Russo, Corrao, 2007, *Am J Nephrol*) assessed the rate and potential determinants of CAC progression in CKD patients (Stages 3 through 5) not requiring dialysis over a two year period. The study included 113 patients (60 with normal renal function and 53 with CKD Stages 3-5) not on dialysis. CAC progression was significantly prominent in 51% of CKD patients (*p*<0.0001). Most patients had CAC scores >400 AU, which is the threshold for high cardiovascular risk. Progression occurred in the absence of significant deterioration of renal function (10% in patients with normal renal function). It was found that CAC progression (above 75th percentile) rates were significantly correlated with higher serum phosphorus levels despite majority of the patients having “normal” levels of phosphorus according to KDOQI (*p*=0.015).

The occurrence of vascular calcification in CKD-pre-dialysis patients has also been reported by Block et al., who observed that approximately 30% of patients showed evidence of vascular calcification (CAC score >400) at onset of dialysis (Block, 2000, *Clin Nephrol*; Block and Port, 2000, *Am J Kidney Dis*). In this study, baseline CAC score, as measured by electron-beam computed tomography, is an independent predictor of mortality in subjects new to hemodialysis (CAC=0; CAC 1 to 400; CAC≥400). This trial confirms the finding that severity of CAC at the time of initiation of hemodialysis is an important predictor of long-term survival (Block, Raggi, 2007, *Kidney Int*).

### 4.3 CKD-MBD: Clinical Features and Treatment

#### 4.3.1 The Continuum of Impaired Kidney Function and Other Symptoms in CKD

CKD is a complex systemic disease encompassing a continuum of clinical features of increasing severity, including progressively reduced GFR, kidney failure up to and including the need for dialysis, abnormal mineral metabolism and serum mineral levels, and disordered bone metabolism and extraskeletal calcification (Fadem and Moe, 2007, *Adv Chronic Kidney Dis*; Moe, Drueke, 2007, *Adv Chronic Kidney Dis*). The Kidney Disease Improving Global Outcomes (KDIGO) group recently established new terms, CKD-Mineral and Bone Disorder (CKD-MBD) and renal osteodystrophy, to acknowledge and describe this complexity (NKF, 2007, *Am J Kidney Dis*).
CKD is classically associated with decreasing kidney function ranging from a mild reduction in GFR accompanied by kidney damage (i.e., Stage 2); to a moderate to severe reduction in GFR regardless of the presence of kidney damage (and the attendant risk of complications [Stages 3 to 4]); to drastically reduced GFR and kidney failure (Stage 5)(NKF, 2007, *Am J Kidney Dis*). Therefore, although CKD-MBD is associated with many abnormalities beyond decreases in GFR, this discussion of clinical features and treatment will focus on those patients classically defined as CKD Stage 3, 4, or 5, that is, those patients with significantly reduced GFR and CKD leading to kidney failure and dialysis.

Table 4-2 summarizes the KDIGO definitions of these terms.

**Table 4-2  KDIGO Classification of CKD-MBD and Renal Osteodystrophy**

| Definition of CKD-MBD                                                                 | • Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism  
|                                                                                   | • Abnormalities in bone turnover, mineralization, volume, linear growth, or strength  
|                                                                                   | • Vascular or other soft-tissue calcification  
| Definition of Renal Osteodystrophy                                               | • An alteration of bone morphology in CKD  
|                                                                                   | • A measure of the skeletal component of the systemic disorder of CKD-MBD that is quantitative by histomorphometry of bone biopsy  

**4.3.2 Morbidity and Mortality of CKD-MBD**

Morbidity and mortality among CKD-MBD patients are as complex as the disease itself, often involving interactions among decreased renal function, cardiovascular disease, and mineral/bone dysregulation. In general, morbidity and all-cause mortality are elevated in CKD-MBD patients relative to the general population, particularly in those with multiple comorbidities such as cardiovascular disease and diabetes, and in those with progressively more severe kidney disease. Hyperphosphatemia and disordered mineral metabolism correlate significantly with morbidity and mortality among patients with Stage 5 disease, including premature death, increased hospitalization, reduced quality of life, and increased cost of care (Levine, 1998, *J Am Soc Nephrol*).

Patients with CKD Stage 4 (GFR 15 to 29 mL/min/1.73m²) have been reported to have a 5-year mortality rate of nearly 50% (Keith, Nichols, 2004, *Arch Intern Med*).

Despite many medical advances, the yearly mortality rate for CKD patients who are receiving dialysis remains at 20% (Foley, Parfrey, 1998, *Am J Kidney Dis*). The expected remaining life span reported by the USRDS on average was 7 to 11 years for dialysis patients aged 40 to 44, and 4 to 6 years for those 60 to 64, which was markedly worse than the expected lifespan of the general population (30 to 40 years for those aged 40 to 44 and 15 to 23 years for those aged 60 to 64). However, over the last few years there is some evidence that mortality rates among patients new to dialysis have been decreasing. This likely reflects improvements in the overall care of this population which in part may be attributed to the establishment of clinical practice guidelines (Baxter and DeLuca, 1976, *J Biol Chem*; Berner and Shike, 1988, *Annu Rev Nutr*; Collins, Kasiske, 2006, *American Journal of Kidney Diseases*; Kinney, 2006, *Am J Kidney Dis*).

### 4.3.2.1 Cardiovascular Mortality and All-Cause Mortality


The all-cause and cardiovascular mortality in CKD is many folds higher than that of matched cohorts without CKD. Individuals with CKD are 5 to 10 times more likely to die before reaching ESRD than non-CKD patients (Collins, Li, 2003, *Kidney Int Suppl*). Among CKD patients, CVD is twice as common and advances at twice the rate compared with non-CKD patients. CVD advances at a similarly higher rate in CKD patients who die and those who survive to ESRD.

Mortality due to cardiovascular disease is 10 to 20 times greater in CKD Stage 5 hemodialysis patients compared to the general population after adjusting for age, race, gender, and the presence of diabetes (Foley, Parfrey, 1998, *Am J Kidney Dis*). Dialysis
patients experience a 16- to 19-fold increased risk for developing myocardial ischemia and infarction when compared to appropriate age- and sex-matched populations without renal failure (Ma, Greene, 1992, *Am J Kidney Dis*).

The presence of diabetes also exacerbates the risk of mortality in patients with CVD and CKD. Those with diabetes as the cause of nephropathy have a 2- to 3-fold increased mortality risk compared to those with non-diabetic renal disease.

In addition to traditional CVD risk factors, non-traditional uremia-related factors unique to renal failure are also thought to significantly contribute to the increased risk of cardiovascular complications in CKD patients (Qunibi, 2004, *Kidney Int Suppl*). These risk factors include the following (Table 4-3):

**Table 4-3 Renal and Non-Renal Associated Cardiovascular Risk Factors**

<table>
<thead>
<tr>
<th>Classic CVD Risk Factors</th>
<th>Uremia-Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>older age</td>
<td>hyperphosphatemia</td>
</tr>
<tr>
<td>male sex</td>
<td>elevated calcium</td>
</tr>
<tr>
<td>hypertension</td>
<td>increased Ca×P product</td>
</tr>
<tr>
<td>diabetes</td>
<td>high iPTH levels</td>
</tr>
<tr>
<td>smoking</td>
<td>vitamin D therapy</td>
</tr>
<tr>
<td>high LDL cholesterol</td>
<td>inflammation (e.g., C-reactive protein)</td>
</tr>
<tr>
<td>low HDL cholesterol</td>
<td>oxidative stress</td>
</tr>
<tr>
<td>hyperhomocysteinemia</td>
<td>malnutrition</td>
</tr>
<tr>
<td>physical inactivity</td>
<td>volume overload</td>
</tr>
<tr>
<td>obesity</td>
<td>chronic anemia</td>
</tr>
<tr>
<td>family history of cardiovascular disease</td>
<td>albuminuria</td>
</tr>
<tr>
<td>left ventricular hypertrophy</td>
<td>endothelial dysfunction</td>
</tr>
<tr>
<td>menopause</td>
<td></td>
</tr>
<tr>
<td>genetic predisposition</td>
<td></td>
</tr>
</tbody>
</table>

4.3.2.1.1 Hyperphosphatemia is an Independent Cardiovascular Risk Factor

Disorders of mineral metabolism, especially hyperphosphatemia, are involved in the pathogenesis of vascular calcification, an active process that begins in early stages of CKD, accelerates in CKD Stage 5, and already is established in many patients at the time of initiation of maintenance dialysis therapy. Disordered mineral metabolism with vascular calcification in turn contributes to the progression of atherosclerosis and cardiovascular events in CKD patients (Kestenbaum and Belozeroff, 2007, *Eur J Clin Invest*; Mehrotra, 2006, *J Ren Nutr*; Mehrotra, Budoff, 2005, *Kidney Int*). Consequently, hyperphosphatemia is now recognized as an independent CVD risk factor contributing to CVD morbidity and mortality (Maschio, Oldrizzi, 1982, *Kidney Int*).

### Table 4-4 Association of Serum Phosphorus Levels with Vascular Calcification and Cardiovascular Events

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Tonelli, Sacks, 2005, <em>Circulation</em>) (Cholesterol and Recurrent Events, CARE)</td>
<td>Non-CKD Prior coronary disease</td>
<td>4,127</td>
<td>Statistically significant graded association with higher phosphorus levels and the risk of death and cardiovascular events in individuals with prior myocardial infarction, most of whom had serum phosphorus levels within the normal range. Those with serum phosphorus levels ≥ 4 mg/dL had a 43% risk for developing heart failure, 50% risk for experiencing myocardial infarction, and 32% risk for experiencing the composite outcome of coronary death or non-fatal myocardial infarction compared to those with serum phosphorus of 2.5 to 3.4 mg/dL.</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, <em>J Am Soc Nephrol</em>)</td>
<td>CKD pre-dialysis</td>
<td>6,730</td>
<td>Each 1-mg increment was associated with a 35% increased risk for myocardial infarction, and a 28% increase in risk for the combined endpoint of death and non-fatal myocardial infarction.</td>
</tr>
</tbody>
</table>
4.3.2.1.1.1 Hyperphosphatemia and Mortality in CKD Stage 5 Patients on Dialysis

Hyperphosphatemia correlates significantly with morbidity and mortality in patients with CKD Stage 5 receiving dialysis, and is associated with premature death, increased hospitalization, reduced quality of life, and increased cost of care (Levine, 1998, *J Am Soc Nephrol*). Data from the USRDS, the Case Mix Adequacy Study (CMAS), and the Dialysis Morbidity and Mortality Study (DDMS) wave 1 found that patients with serum phosphorus levels >6.5 mg/dL had a 27% higher mortality risk (RR=1.27) than patients with phosphorus levels from 2.4 to 6.5 mg/dL (Block and Port, 2000, *Am J Kidney Dis*). A Ca x P product >72 mg²/dL² was associated with a significantly higher relative risk of death (RR = 1.34) (Block and Port, 2000, *Am J Kidney Dis*). These results correlate well with previously published data suggesting an increased risk of metastatic calcification at Ca x P levels above 60 to 75 mg²/dL² (Krolewski, Warram, 1994, *Kidney Int Suppl*; Slatopolsky, Caglar, 1971, *J Clin Invest*). Analysis of a large database of more than 40,000 patients undergoing hemodialysis in the US showed an association with increased mortality for phosphorus levels greater than 5.0 mg/dL, with a progressive increase in mortality at increasing levels of serum phosphorus (Block, Klassen, 2004, *J Am Soc Nephrol*).

The following table (Table 4-5) lists a number of studies describing the association of hyperphosphatemia and morbidity/mortality, which are described in more detail below.
Table 4-5   Serum Phosphorus Levels and Clinical Outcomes in CKD Stage 5

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lowrie and Lew, 1990, <em>Am J Kidney Dis</em>)</td>
<td>Hemodialysis patients</td>
<td>&gt;12,000</td>
<td>Phosphorus is a significant predictor of mortality.</td>
</tr>
<tr>
<td>(Block, Hulbert-Shearon, 1998, <em>Am J Kidney Dis</em>)</td>
<td>Hemodialysis patients</td>
<td>6,400</td>
<td>RR of death after adjustment for cardiovascular risk factors was 1.27 compared with patients with serum phosphorus concentrations of 2.4 to 6.5 mg/dL.</td>
</tr>
<tr>
<td>(Levine, 1998, <em>J Am Soc Nephrol</em>)</td>
<td>Hemodialysis patients</td>
<td>6,407</td>
<td>RR of 1.56 for death from coronary artery disease (CAD) in patients with serum phosphorus concentrations &gt;6.5 mg/dL compared with patients with lower values. The RR of sudden death, generally considered to be of cardiac origin (e.g., dysrhythmia), was 1.27. For every 10 mg²/dL² increase in the Ca × P product, the RR of sudden death increased 1.11.</td>
</tr>
<tr>
<td>(Ganesh, Stack, 2001, <em>J Am Soc Nephrol</em>)</td>
<td>Hemodialysis patients</td>
<td>7,096</td>
<td>In patients with a serum phosphorus concentration &gt;6.5 mg/dL, the mortality risk was significantly higher than that in patients with lower phosphorus concentrations (≤ 6.5 mg/dL) for death resulting from CAD (RR 1.41, p&lt; 0.0005), sudden death (RR 1.20, p&lt;0.01), infection (RR1.20, p&lt;0.05), and unknown causes (RR 1.25, p&lt; 0.05).</td>
</tr>
<tr>
<td>(Block, Klassen, 2004, <em>J Am Soc Nephrol</em>)</td>
<td>Hemodialysis patients</td>
<td>40,538</td>
<td>Serum phosphorus &gt;5.0 mg/dL were associated with an increased relative risk of death. Hyperphosphatemia were significantly associated with all-cause, cardiovascular, and fracture-related hospitalization.</td>
</tr>
<tr>
<td>(Young, Albert, 2005, <em>Kidney Int</em>)(DOPPS)</td>
<td>Hemodialysis patients</td>
<td>17,236</td>
<td>All-cause mortality was significantly and independently associated with serum phosphorus (RR 1.04 per mg/dL, p=0.0003). Cardiovascular mortality was significantly associated with serum phosphorus (RR1.17, p&lt; 0.0001).</td>
</tr>
</tbody>
</table>

Lowrie and Lew first noted a significant association between hyperphosphatemia and higher mortality rates in hemodialysis patients (Lowrie and Lew, 1990, *Am J Kidney Dis*). The study identified serum phosphorus as a predictor for mortality in hemodialysis patients. This original work also identified hypoalbuminemia as a predictor of mortality in this population. The association of hypoalbuminemia and mortality was considered such a major finding at the time that the relationship between hyperphosphatemia and mortality received little attention.

A landmark study by Block et al. (Block, Hulbert-Shearon, 1998, *Am J Kidney Dis*) assessed the level at which serum phosphorus was a mortality risk using data from 6,400 dialysis...
patients from the USRDS Case Mix Adequacy Study (CMAS) and the Dialysis Morbidity and Mortality Wave 1 (DMMS). The study reported that in patients with serum phosphorus concentrations $>6.5\, \text{mg/dL}$, the RR of death after adjustment for cardiovascular risk factors was 1.27 compared with patients with serum phosphorus concentrations of 2.4 to 6.5 mg/dL. There also was a correlation between the Ca x P product and death, the RR being 1.34 for patients with products $>72\, \text{mg}^2/\text{dL}^2$ versus those with a value of 42 to 52 mg$^2$/dL$^2$.

Levine et al. found a RR of 1.56 for death from CAD in patients with serum phosphorus concentrations $>6.5\, \text{mg/dL}$ compared with patients with lower values (Levine, 1998, J Am Soc Nephrol). The RR of sudden death, generally considered to be of cardiac origin (e.g., dysrhythmia), was 1.27. For every 10 mg$^2$/dL$^2$ increase in the Ca x P product, the RR of sudden death increased 1.11 (Levine, 1998, J Am Soc Nephrol).

Ganesh et al. described an analysis of data from the Case Mix Adequacy Study (7,096 hemodialysis patients who were alive at the end of 1990) and the Dialysis Morbidity and Mortality Study (15,548 hemodialysis patients who were alive at the end of 1993) (Ganesh, Stack, 2001, J Am Soc Nephrol). During the 2-year follow-up, there were 4,120 deaths, of which 752 (18%) were caused by coronary artery or other cardiac disease and 1,111 (27%) were sudden deaths. In patients with a serum phosphorus concentration $>6.5\, \text{mg/dL}$, the mortality risk was significantly higher than that in patients with lower phosphorus concentrations ($\leq 6.5\, \text{mg/dL}$) for death resulting from CAD (RR 1.41, $p<0.0005$), sudden death (RR 1.20, $p<0.01$), infection (RR 1.20, $p<0.05$), and unknown causes (RR 1.25, $p<0.05$).

In an analysis of 40,538 hemodialysis patients from a large dialysis organization, Block et al. evaluated the associations among mineral metabolism disorders with mortality and morbidity in patients who had at least one determination of serum phosphorus and calcium (Block, Klassen, 2004, J Am Soc Nephrol). After adjustments for case mix and laboratory variables, serum phosphorus levels $>5.0\, \text{mg/dL}$ were associated with an increased relative risk of death (1.07; 1.25; 1.43; 1.67; and 2.02 for serum phosphorus levels of 5.0 to 6.0; 6.0 to 7.0; 7.0 to 8.0; 8.0 to 9.0; and $\geq 9.0\, \text{mg/dL}$, respectively). When analyzed collectively, the population’s attributable risk for disorders of mineral metabolism was 17.5%, owing largely to the high prevalence of hyperphosphatemia. It was also found that hyperphosphatemia was significantly associated with all-cause, cardiovascular, and fracture related hospitalization.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) evaluated the associations between mineral metabolic abnormalities and mortality for 17,236 hemodialysis patients in the US, Europe, and Japan. It was found that serum phosphorus was significantly and
independently associated with all-cause mortality (RR 1.04 per 1 mg/dL, \( p=0.0003 \)) and cardiovascular mortality (RR 1.09 per 1 mg/dL, \( p<0.0001 \)) (Young, Albert, 2005, *Kidney Int*).

Across a number of additional studies, the documented threshold of serum phosphorus concentration for a significant increased risk ranges from 3.5 to >6.5 mg/dL, and when analyzed as a continuous variable a 1 mg/dL increment in the serum phosphorus concentration is associated with a 4% to 9% higher mortality risk (Young, 2007, *Adv Chronic Kidney Dis*). It is estimated that correction of hyperphosphatemia could save nearly 34,000 patient life years in the US over a 5-year period (Port, Pisoni, 2004, *Blood Purif*; Young, 2007, *Adv Chronic Kidney Dis*).

### 4.3.2.1.1.2 Hyperphosphatemia and Mortality in Pre-Dialysis

Since the publication of the KDOQI clinical guidelines in 2003, at least six large-scale studies have shown an association of phosphorus retention and mortality and/or progression of kidney disease in CKD patients, including pre-dialysis and non-CKD individuals (Kestenbaum, Sampson, 2005, *J Am Soc Nephrol*; Menon, Greene, 2005, *Am J Kidney Dis*). A large body of evidence suggests a causal link between serum phosphorus concentration and mortality in CKD. These data also provide evidence that phosphorus retention is associated with increased risk of cardiovascular calcification, morbidity, and mortality. The following studies provide evidence that phosphorus retention is associated with increased risk of mortality:
To assess the relationship between high serum phosphorus levels and mortality risk in CKD patients, Kestenbaum et al. studied a cohort of 6,730 US veterans with CKD of which 67% had CKD Stage 3 (Kestenbaum, Sampson, 2005, *J Am Soc Nephrol*). The primary outcome was all-cause mortality, and secondary outcomes were hospitalizations, acute myocardial infarction (MI), and the combined endpoint of death plus MI. Serum phosphorus levels increased marginally with declining estimated creatinine clearance (CrCl). At CrCl ≤30 mL/min (Stages 4 and 5), mean phosphorus levels increased rapidly even though the phosphate levels were within the normal ranges for earlier CKD Stages. Approximately 46% of CKD Stage 4 patients died before reaching dialysis, consistent with previous observations (Go, Chertow, 2004, *N Engl J Med*; Keith, Nichols, 2004, *Arch Intern Med*; Shulman, Ford, 1989, *Hypertension*). After adjustment, serum phosphate levels >3.5 mg/dL were associated with a significantly increased risk for death. Mortality risk increased linearly with each subsequent 0.5 mg/dL increase in serum phosphorus levels. Elevated serum phosphorus levels were independently associated with increased mortality risk among the cohort with

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Voormolen, Noordzij, 2007, <em>Nephrol Dial Transplant</em>) (PREPARE)</td>
<td>CKD pre-dialysis (eGFR 13 mL/min/1.73m²)</td>
<td>547</td>
<td>High serum phosphorus is an independent risk factor for death. Mortality risk was 25% per mg/dL in serum phosphorus which increased to 62% after adjustment.</td>
</tr>
<tr>
<td>(Tonelli, Sacks, 2005, <em>Circulation</em>) (CARE)</td>
<td>Non-CKD Prior coronary disease</td>
<td>4,127</td>
<td>Significant, graded, independent relation between higher serum phosphorus and the risk of death. Phosphorus ≥4 mg/dL had a significantly 32% increase risk for all-cause mortality when compared to phosphorus levels between 2.5 and 3.4 mg/dL, The group with baseline values ≥3.5 mg/dL had a significantly 27% increase risk for all-cause mortality when compared to phosphorus levels &lt; 3.5 mg/dL.</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, <em>J Am Soc Nephrol</em>)</td>
<td>CKD pre-dialysis</td>
<td>6,730</td>
<td>After a median follow-up of 2.1 years, 32.5% had died, 7.4% reached ESRD and 4.5% were lost to follow-up. It was estimated that for each 1 mg/dL (0.323 mmol/L) increase in serum phosphorus, there was a 23% increased risk of death. There was a statistically significant increase in mortality risk associated with phosphorus levels &gt; 3.5 mg/dL.</td>
</tr>
</tbody>
</table>
CKD. It was estimated that for each 1 mg/dL (0.323 mmol/L) increase in serum phosphorus there was a 23% increased risk of death.

In the Cholesterol and Recurrent Events (CARE) study (discussed above), involving 4,127 patients with serum phosphorus levels, Tonelli et al. found that there was a statistically significant graded association between baseline phosphorus levels and the various mortality and morbidity endpoints (Tonelli, Sacks, 2005, *Circulation*). The group with baseline serum phosphorus values ≥4 mg/dL had a significantly higher frequency of all-cause mortality (fully adjusted hazard ratio FAHR, 1.32) when compared with the group that had values between 2.5 and 3.4 mg/dL. In addition, the group with baseline serum phosphorus values ≥3.5 mg/dL had a significantly higher frequency of all-cause mortality (adjusted HR, 1.27) when compared to the group with baseline values <3.5 mg/dL.

More recently, a retrospective follow-up study of 547 incident pre-dialysis patients in the Netherlands assessed the association of plasma phosphorus with decline in renal function and mortality risk in incident pre-dialysis patients (CKD Stage 4–5 with GFR <20 mL/min/1.73 m²). It concluded that high plasma phosphorus is an independent risk factor for a more rapid decline in renal function and a higher mortality during the pre-dialysis phase (Voormolen, Noordzij, 2007, *Nephrol Dial Transplant*) (Table 4-7). It was estimated that mortality risk was 25% per mg/dL in serum phosphorus, which increased to 62% after adjustment. Plasma phosphorus within the normal range is likely to be of clinical importance in pre-dialysis patients.
Table 4-7  Association of Phosphate and Calcium Phosphate Product with Rate of Decline in Renal Function and Mortality

<table>
<thead>
<tr>
<th>Decline</th>
<th>Crude β (per ml/min/month decline)</th>
<th>P</th>
<th>Adjusted β (per ml/min/month decline)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate, mg/dl²</td>
<td>0.154 (0.071-0.237)</td>
<td>&lt;0.001</td>
<td>0.178 (0.082-0.275)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ca × phosphate, mg²/dl²</td>
<td>0.015 (0.006-0.023)</td>
<td>0.001</td>
<td>0.018 (0.008-0.028)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium, 0.1 mg/dl²</td>
<td>−0.029 (−0.153– 0.095)</td>
<td>0.645</td>
<td>0.051 (−0.077–0.180)</td>
<td>0.430</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Crude RR (95% CI)</th>
<th>P</th>
<th>Adjusted RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate, mg/dl²</td>
<td>1.25 (0.85–1.84)</td>
<td>0.262</td>
<td>1.62 (1.02–2.59)</td>
<td>0.042</td>
</tr>
<tr>
<td>Ca × phosphate, mg²/dl²</td>
<td>1.03 (0.99–1.07)</td>
<td>0.173</td>
<td>1.06 (1.01–1.11)</td>
<td>0.019</td>
</tr>
<tr>
<td>Calcium, 0.1 mg/dl²</td>
<td>1.11 (0.91–1.35)</td>
<td>0.347</td>
<td>1.32 (0.69–2.51)</td>
<td>0.400</td>
</tr>
</tbody>
</table>

* A negative β is equivalent to an improvement in renal function; Ca × phosphate, Calcium × phosphate.

1 mg/dl change in plasma phosphate is equivalent to 0.32 mmol/l change.

1 mg/dl change in plasma calcium is equivalent to 0.25 mmol/l change.

* adjusted for age, gender, primary kidney disease, baseline eGFR, systolic blood pressure, proteinuria, Hb and serum calcium.

* adjusted for age, gender, primary kidney disease, baseline eGFR, systolic blood pressure, proteinuria and Hb.

* adjusted for age, gender, primary kidney disease, baseline eGFR, systolic blood pressure, proteinuria, Hb and plasma phosphate.

* adjusted for age, gender, primary kidney disease, baseline eGFR and comorbidity at baseline (diabetes, cardiovascular disease, malignancy and pulmonary disease).

Reference: (Voormolen, Noordzij, 2007, Nephrol Dial Transplant)

These observations have heightened the focus on therapies that lower phosphorus burden.

Treatment targets for serum phosphorus have been established in the CKD Stage 5 dialysis population based on multiple findings supporting serum phosphorus level as an independent predictor of morbidity and mortality. As a result, new treatment targets to normalize serum phosphorus levels prior to dialysis in CKD are now recommended (NKF, 2003, Am J Kidney Dis).

4.3.2.1.3 Cardiovascular Disease and Serum Phosphorus Levels in Upper Range of Normal

While the association of hyperphosphatemia and adverse cardiovascular outcomes is well recognized, there are emerging data that indicate an association of cardiovascular events and serum phosphorus levels in the upper range of normal.

Tonelli et al. (Tonelli, Sacks, 2005, Circulation) reported a graded, independent relation between baseline serum phosphorus levels and the risk of death, development of new heart failure, and coronary events in non-CKD individuals with prior myocardial infarction, most of whom had serum phosphorus levels within the normal range. Patients were followed for five years. The group with baseline values ≥3.5 mg/dL had a significantly higher frequency of all-cause mortality (adjusted HR, 1.27) when compared to the group with baseline values <3.5 mg/dL.
Another study of 3,368 Framingham Offspring Study participants (Dhingra, Sullivan, 2007, *Arch Intern Med*) of equal gender distribution (mean age: 44 years) followed these subjects for 20 years and found a significant association of high serum phosphorus levels with cardiovascular disease risk (myocardial infarction, angina, congestive heart failure, sudden cardiac death, cerebrovascular disease, and peripheral vascular disease). Higher serum phosphorus levels were associated with an increase in cardiovascular risk in a continuous fashion (adjusted hazard ratio per increment of mg/dl, 1.31; CI, 1.05-1.63; p=0.02; trend across quartiles, p=0.004). These associations remained robust even when cardiovascular disease risk factors were updated every four years and when data analyses were restricted to subjects without proteinuria and eGFR >90 mL/min/1.73 m². These observations emphasize the link of phosphorus homeostasis and vascular risk.

**Table 4-8 Serum Phosphorus Levels and Clinical Outcome in CKD and Non-CKD**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Number</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Norris, Greene, 2006, <em>J Am Soc Nephrol</em>) (AASK)</td>
<td>CKD (GFR 20-65 mL/min/1.73m²)</td>
<td>1,094</td>
<td>Elevated phosphorus is directly associated with clinical renal events (50% or 25-mL/min GFR decline or CKD Stage 5) and death</td>
</tr>
<tr>
<td>(Voormolen, Noordzij, 2007, <em>Nephrol Dial Transplant</em>) (PREPARE)</td>
<td>CKD pre-dialysis (eGFR 13 mL/min/1.73m²)</td>
<td>448</td>
<td>High serum phosphorus is associated with more rapid decline in renal function and higher mortality rate</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, <em>J Am Soc Nephrol</em>)</td>
<td>CKD (CrCl 45.1mL/min)</td>
<td>3,490</td>
<td>Mortality risk increased linearly with every 0.5-mg/dL increase in serum phosphorus, starting at 3.5 mg/dL</td>
</tr>
<tr>
<td>(Dhingra, Sullivan, 2007, <em>Arch Intern Med</em>)</td>
<td>Non-CKD Non-CVD</td>
<td>3,368</td>
<td>Serum phosphorus &gt;3.5 mg/dL are associated with increased risk of CVD in a graded fashion</td>
</tr>
<tr>
<td>(Tonelli, Sacks, 2005, <em>Circulation</em>) (CARE)</td>
<td>Non-CKD Prior coronary disease</td>
<td>4,127</td>
<td>Serum phosphorus &gt;3.5 mg/dL are associated with increased risk of death and cardiovascular events in a graded fashion</td>
</tr>
</tbody>
</table>

### 4.3.2.1.2 Progression of Renal Disease

In patients with severe CKD, the percentage of preserved renal function not only delays dialysis, but once dialysis is initiated, the residual renal function is associated with survival as well (Termorshuizen, Dekker, 2004, *J Am Soc Nephrol*). Several risk factors for more rapid progression of renal function loss have been identified, including primary kidney disease, race, baseline renal function, proteinuria, blood pressure, poor glycemic control, smoking, and, possibly, also dyslipidemia and anemia. (NKF, 2002, *Am J Kidney Dis*) In addition to these factors, plasma phosphate is a potential risk factor for a more progressive


Large epidemiological studies, summarized Table 4-9 and presented in more detail below, supports a direct association between hyperphosphatemia and progression of renal disease, clinical renal events, and mortality.
Table 4-9  Serum Phosphorus Levels and Progression of Renal Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>n</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Voormolen, Noordzij, 2007, Nephrol Dial Transplant) (PREPARE)</td>
<td>CKD pre-dialysis (eGFR 13 mL/min/1.73m²)</td>
<td>547</td>
<td>High serum phosphorus is associated with more rapid decline in renal function.</td>
</tr>
<tr>
<td>(Sigrist, Bungay, 2006, Nephrol Dial Transplant)</td>
<td>CKD Stages 1-5</td>
<td>985</td>
<td>High serum phosphorus is associated with progression to CKD Stage 5 and doubling of serum Cr in a graded fashion.</td>
</tr>
<tr>
<td>(Norris, Greene, 2006, J Am Soc Nephrol) (AASK)</td>
<td>CKD (GFR 20-65 mL/min/1.73m²)</td>
<td>1,094</td>
<td>Elevated serum phosphorus was significantly associated with an increased risk for a decline in GFR by 50% or 25 mL/min/1.73m² or progression to ESRD.</td>
</tr>
<tr>
<td>(Dellegrottaglie, Saran, 2006, Am J Cardiol)</td>
<td>Stages 3-5 CKD pre-dialysis (eGFR &lt; 50 mL/min/1.73m²)</td>
<td>106</td>
<td>Even though the extent of CAC in pre-dialysis CKD patients was not to indices of abnormal renal function or progression in renal dysfunction, higher serum phosphorus, iPTH, and diabetes status were significantly associated with decreasing renal function (p=0.035).</td>
</tr>
<tr>
<td>(Kestenbaum, Sampson, 2005, J Am Soc Nephrol)</td>
<td>CKD pre-dialysis</td>
<td>6,730</td>
<td>Marked increases in mean phosphorus levels when GFR levels fell below 30 mL/min/1.73 m² (Stage 4).</td>
</tr>
</tbody>
</table>

In a study of 1,094 CKD patients with GFR 20-65 mL/min/1.73m², Norris et al. examined factors that predict increased risk for adverse renal outcomes using Cox regression analysis to assess the potential of 38 risk factors to predict the clinical renal composite outcome of 50% or 25 mL/min/1.73m² GFR decline or CKD Stage 5 among black hypertensive patients. They found that serum phosphorus was significantly associated with an increased risk for renal outcomes (Norris, Greene, 2006, J Am Soc Nephrol).

One large cohort study (PREPARE study) (Voormolen, Noordzij, 2007, Nephrol Dial Transplant) of pre-dialysis patients (N=547), demonstrated a correlation of plasma phosphate level with faster deterioration of renal function, independent of absolute renal function. For each mg/dL higher serum phosphate concentration, the mean (95% CI) decline in renal function increased by 0.154 (0.071-0.237) mL/min/month. An increased mortality risk was associated with a high plasma phosphate concentration (Voormolen, Noordzij, 2007, Nephrol Dial Transplant). Although the crude risk was 1.25, after correction for primary cause of kidney disease and comorbidities, this risk increased to 1.62 for each mg/dl increase in plasma phosphate concentration independent of age and gender (Voormolen, Noordzij, 2007, Nephrol Dial Transplant). This corrected mortality risk is higher than the 1.33 mg/dl found...

Schwarz et al. 2006 (Schwarz, Trivedi, 2006, *Clin J Am Soc Nephrol*) investigated the association of baseline levels of serum phosphorus, calcium, and Ca x P product with renal function outcomes in a well characterized cohort of 985 male US veterans who had CKD Stages 1 through 5 and were not yet on dialysis (Schwarz, Trivedi, 2006, *Clin J Am Soc Nephrol*). The study followed these patients for a median duration of 2.1 years and found an increased risk for progressive CKD (composite of CKD Stage 5 or doubling of serum creatinine) with serum phosphorus levels >3.8 mg/dL (hazard ratio, 1.24) and Ca x P product >40 mg²/dL² (HR, 1.37). Higher serum phosphorus was associated with significantly higher risk for progression of CKD, even after adjustment for multiple potential confounders (Schwarz, Trivedi, 2006, *Clin J Am Soc Nephrol*). In the same study, investigators found that a higher Ca x P product was associated with more progressive CKD and a significant quantitative interaction between serum phosphorus and calcium levels. Higher serum phosphorus was strongly associated with a higher risk for progression to CKD Stage 5 and doubling of serum creatinine.
Figure 4-6  Hazard Ratio of the Composite Outcome of ESRD and Doubling of Serum Creatinine Associated with Various Quartiles of Serum Phosphorus Unadjusted and Adjusted

![Graph showing hazard ratio](image)

Each 1 mg/dL increment of serum phosphorus and each 10 mg²/dL² increment of Ca x P product was associated with a hazard ratio of 1.29. In all, 210 patients reached the endpoint of CKD Stage 5, while an additional 48 patients reached the endpoint of doubling of serum creatinine. The subpopulation with phosphorus levels >4.3 mg/dL (hazard ratio, 1.60) comprised a higher percentage of diabetics, active smokers, lower eGFR, lower hemoglobin, lower serum albumin, lower calcium, and lower bicarbonate, and greater degree of proteinuria. The authors concluded that elevated phosphorus was behaving as an independent risk factor rather than surrogate in this study. The association of higher serum phosphorus with progressive CKD was especially prominent in patients with concomitant higher calcium levels, supporting the hypothesis that nephrocalcinosis may be the reason for the observed association with progressive CKD.

There is now a large body of epidemiological evidence linking the common disturbances of bone and mineral metabolism with increased risk of death, primarily due to increased risk of cardiovascular death. The most commonly reported association is the direct relationship between serum phosphorus and the relative risk of death, has now been replicated in several large studies of different populations, with different study designs and investigators.

The association between serum phosphorus and mortality does not necessarily prove a causal relationship. Mortality could be related to other factors such as comorbidity or non-compliance. Young has pointed out that although this is a possibility, three factors suggest a causal relationship: (1) The results have been replicated in several large studies using
different populations and study designs; (2) Each of those studies used multivariate-regression techniques to adjust for many potential confounding variables; and (3) The epidemiologic data are consistent with other observational and experimental data suggesting plausible biologic mechanisms (Young, 2007, *Adv Chronic Kidney Dis*). Therefore, a causal link between serum phosphorus concentration and mortality of CKD seems likely.

### 4.4 Conclusion

Elevated phosphorus is an independent risk factor for CKD-MBD and is a key element driving these abnormalities. Phosphorus directly stimulates vascular calcification. In conclusion, analysis of data from a number of large patient databases including USRDS, the CMAS, and the DOPPS, and from several clinical studies in patients with CKD, indicate a significant relationship between serum phosphorus levels and mortality.
5. CURRENT TREATMENT

5.1.1 Screening for CKD-MBD

CKD screening should be given the highest priority for patients at the highest risk based on comorbidities such as hypertension, diabetes, and cardiovascular disease. In addition, screening should be considered for patients with dyslipidemia, obesity, metabolic syndrome, smokers, and a family history of CKD (NKF, 2002, *Am J Kidney Dis*).

Bone disease and disorders of calcium and phosphorus metabolism develop during the course of CKD and are associated with adverse outcomes. Patients with GFR <60 mL/min/1.73m$^2$ should be evaluated for bone disease and disorders of calcium and phosphorus metabolism.

5.1.2 KDOQI Guidelines

In recognition of the complex nature of CKD as it relates to both causal co-morbidities and adverse outcomes, the KDOQI Working Group has issued a number of clinical practice guidelines for treatment of CKD. The guidelines with particular relevance to this review are listed below. All were published by the NKF in the American Journal of Kidney Diseases.

- Clinical Practice Guidelines For Bone Metabolism and Disease In Chronic Kidney Disease (NKF, 2003, *Am J Kidney Dis*)
- Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients, Overview of Epidemiology of Cardiovascular Disease (NKF, 2005, *Am J Kidney Dis*)

5.1.3 The Role of Phosphorus Control in CKD-MBD Treatment

5.1.3.1 KDOQI Guidelines for Phosphorus Control

Hyperphosphatemia is considered “the silent killer” in CKD patients, and its successful management remains a challenge (Sonikian, Metaxaki, 2006, *Ren Fail*). Considerable evidence supports associations between metabolic consequences of hyperphosphatemia, worsening hyperparathyroidism, and bone disease. As described previously (Section 4.3),
failure to control hyperphosphatemia and the associated physiological abnormalities is associated with debilitating sequelae and increased mortality.

The KDOQI guidelines recommend, based on evidence and expert opinion, that serum phosphorus should be maintained at a level of 2.7 to 4.6 mg/dL for CKD Stage 3-4 patients (i.e., chronic renal insufficiency, GFR 59-29 mL/min/1.73m²) and at 3.5 to 5.5 mg/dL for CKD Stage 5 patients (i.e., pre-end stage renal failure, GFR <15 mL/min/1.73m² OR dialysis)(NKF, 2003, Am J Kidney Dis). The following table summarizes the opinion and recommendations of KDOQI regarding the management of phosphorus levels in such patients.

Table 5-1  KDOQI Treatment Guidelines

<table>
<thead>
<tr>
<th>KDOQI Mineral Parameters</th>
<th>KDOQI Goals</th>
<th>KDOQI Recommendations</th>
</tr>
</thead>
</table>
| Phosphorus               | Stage 3 and 4: 2.7 – 4.6 mg/dL  
                          | Stage 5: 3.5 – 5.5 mg/dL | Stages 3-5  
                          | 1. Restrict dietary phosphorus to 800 to 1,000 mg/day (adjusted for dietary protein needs).  
                          | 2. Phosphate binders initiated if serum phosphorus cannot be controlled by phosphorus restriction.  
                          | 3. Serum phosphorus levels should be monitored every month |

Reference: (NKF, 2003, Am J Kidney Dis)

5.1.3.2 Restriction of Phosphorus on CKD


Dietary restriction of phosphorus was subsequently shown to retard functional deterioration and reduce histologic damage in experimental immunologic renal disease (Karlinsky, Haut, 1980, Kidney Int). Phosphorus restriction initiated 30 days after the administration of nephrotoxic serum in rats prevents renal calcification, histologic damage and functional deterioration and improved survival but has no apparent effect on proteinuria.
Reports of studies in patients demonstrate that dietary restriction of phosphorus can delay but to not prevent progression of functional deterioration in renal failure. Patients with moderate to advanced chronic renal failure on a dietary restriction of protein and phosphorus for up to six years versus showed statistically significant differences in serum creatinine concentrations versus those that were not (Maschio, Oldrizzi, 1982, *Kidney Int*). In a second study (Barsotti, Morelli, 1983, *Kidney Int Suppl*) of 20 renal patients creatinine clearance decreased by $0.59 \pm 0.7$ mL/min/month prior to the commencement of the experimental diet and increased by a mean of $0.1 \pm 0.4$ mL/min/month during the 11-month period of the study versus the 19 renal patients in the control group, the mean creatinine clearance continued to decrease at a rate not significantly different from that prior to the onset of the study. A third study (Barsotti, Giannoni, 1984, *Clin Nephrol*) demonstrated that residual kidney function in chronic renal patients is better maintained if the phosphorus intake is reduced below the limits that are usually achieved by simply lowering protein intake. The Modification of Diet in Renal Disease (MDRD) study did not demonstrate a difference between low protein and standard protein diet on the primary analysis. However, effects of protein restriction in the group of patients with the most rapid deterioration of GFR suggested that low protein intake could have some modifying effects on progression of renal disease (Levey, Adler, 1996, *Am J Kidney Dis*).

### 5.1.3.3 Phosphate Binders

The use of agents to bind phosphorus (i.e., PhosLo, Renagel, and Fosrenol, see Sections 9.1, 9.2, and 9.3) before its absorption in the intestine has been considered a biologically appropriate means of restoring phosphate balance by downregulating PTH secretion. Phosphate binder therapy is used in combination with dietary phosphorus restrictions and urinary clearance/or dialytic clearance to restore acceptable phosphorus concentrations. The phosphate binders currently approved for hemodialysis patients include calcium acetate, lanthanum carbonate, and sevelamer hydrochloride.

Hyperphosphatemia manifests prior to CKD Stage 5 and the need for renal replacement therapy. To that end, the NKF recommends the treatment of hyperphosphatemia with phosphate binders prior to the initiation of dialysis to maintain phosphorus levels within the target range of 2.7 to 4.6 mg/dL in patients with CKD Stages 3 and 4 (NKF, 2003, *Am J Kidney Dis*) if dietary phosphate restriction and dialysis are not sufficient. The use of phosphate binders have been evaluated in pre-dialysis CKD patients and have demonstrated to be effective in controlling hyperphosphatemia (Borrego, Perez del Barrio, 2000, *Nefrologia*; Moriniere, Djerad, 1992, *Nephron*; Wallot, Bonzel, 1996, *Pediatr Nephrol*).
Furthermore, market research suggests that almost 50% of the pre-dialysis CKD patients are currently prescribed phosphate binder therapy for the treatment of hyperphosphatemia.

5.1.4 Modification of Practice Standards

The NKF has recently recommended that hyperphosphatemia is treated prior to the initiation of dialysis. This stems from an understanding of the considerations described above, namely

- indications that hyperphosphatemia manifests in early stages of CKD
- the growing understanding of the adverse outcomes associated with hyperphosphatemia, including elevated morbidity and mortality prior to full renal failure (i.e., prior to Stage 5 kidney disease)
- recognition of hyperphosphatemia as an independent cardiovascular risk factor contributing to cardiovascular morbidity and mortality

Indeed, the KDOQI guidelines recommend that monitoring for disordered mineral metabolism should begin in patients with CKD Stage 3, and that serum phosphorus should be maintained within the target range of 2.7 to 4.6 mg/dL in patients with CKD Stages 3 and 4 or 3.5 to 5.5 mg/dL for CKD Stage 5 (NKF, 2003, Am J Kidney Dis).

This updated public health approach, including earlier identification of patients with early kidney disease and more aggressive treatment strategies, aims to reduce the clinical consequences of hyperphosphatemia and may decrease or delay cardiovascular morbidity and mortality. According to NKF, “prevention of the disturbances in mineral and bone metabolism and their management early in the course of chronic kidney disease are extremely important in improving patients’ quality of life and longevity” (NKF, 2003, Am J Kidney Dis). However, despite clinical treatment guidelines recommending treatment of hyperphosphatemia in earlier stages of CKD (i.e., in pre-dialysis patients), no phosphate binders are currently approved for use in this population. Since CKD represents a continuum of progressive renal dysfunction and increased phosphorus body burden has been identified long before reaching CKD Stage 5, it seems logical to advocate earlier treatment of hyperphosphatemia and extension of the indications for use of phosphate binders to CKD Stages 3 and 4.

5.1.5 Outcomes Study in the CKD Population: Availability and Challenges

There are limited data evaluating the relationship between serum phosphorus levels with all-cause and CVD mortality in patients with earlier stages of CKD. The lack of outcomes data
in the CKD population can be attributed to the following challenges in conducting such a study:

- An outcomes trial would entail a complex study design, requiring the investigators to account for many confounding variables such as age, sex, race, comorbid conditions, laboratory values, and concomitant medications in order to explore the true effect of normalizing serum phosphorus levels in the CKD population and improving all-cause and CVD outcomes while holding these confounding variables constant.

- An outcomes trial would require a large number of patients and a long follow-up time in order to demonstrate statistical significance on the effects of normalizing serum phosphorus levels since many CKD patients have several comorbid conditions and concomitant medications, making compliance and enrollment in the study difficult.

- An outcomes trial design would require the evaluation of normalizing serum phosphorus with the use of phosphate binders compared to a control. It is estimated that at least 50% of the nephrologists in the US are treating CKD patients with phosphate binder therapies as a result of a growing body of evidence in the literature indicating an association between hyperphosphatemia and mortality and the recommendations from KDOQI and KDIGO advocating the benefits of early treatment in this population. It is been estimated that the correction of hyperphosphatemia could save approximately 34,000 patient life-years in the US over a 5-year period (Port, Pisoni, 2004, *Blood Purif*; Young, 2007, *Adv Chronic Kidney Dis*). Thus, concerns about deviating from best clinical practices would also compound the difficulties involved with recruiting a large number of patients required in such an outcomes trial from both the healthcare professionals’ and patients’ perspectives.

The evidence that links mortality with altered mineral metabolism is compelling and growing. The all-cause and CVD mortality for ESRD is unacceptably high, especially in the US. Despite the limitations of outcomes data in the CKD population, the management of hyperphosphatemia with phosphate binders provides an alternative for improving mortality in this patient population.
6. EVALUATION OF BENEFITS AND RISKS OF PHOSPHATE BINDER THERAPY FOR HYPERPHOSPHATEMIA IN PATIENTS WITH CKD NOT ON DIALYSIS THERAPY

6.1 Expanded Indication

The three companies that currently market phosphate binders (Fresenius Medical Care, Genzyme Corporation, and Shire Pharmaceuticals) believe that there is sufficient evidence to support expanding the current indication for phosphate binders to control of hyperphosphatemia in CKD patients prior to and following the initiation of dialysis.

6.2 Summary of Benefits and Risks

Table 6-1 Benefits and Risks of Phosphate Binder Therapy in CKD Patients not on Dialysis

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early and sustained reduction of serum phosphate levels to within normal range to prevent or attenuate Calciphylaxis</td>
<td>Adverse Events (AEs)</td>
</tr>
<tr>
<td>Vascular Calcification</td>
<td>GI events common, mild and transient</td>
</tr>
<tr>
<td>Progression of decline in GFR</td>
<td>Hypophosphatemia: rare if nutrition is maintained</td>
</tr>
<tr>
<td>Complications related to CKD-MBD</td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td>Use with active vitamin D and vitamin D supplements</td>
<td>Antacid precautions: dissociate intake of other drugs from phosphate binder by 2 hours.</td>
</tr>
<tr>
<td>Benefits of early treatment may have impacts on morbidity and mortality</td>
<td>May be product specific -DDI clinical pharmacology studies</td>
</tr>
</tbody>
</table>

An important next step for the management of patients with CKD will be to integrate the control of hyperphosphatemia for CKD bone and vascular disease with the management of the other CKD specific therapies (active vitamin D, and erythropoietin). The prevention of extraskeletal calcifications and cardiovascular complications of uremia will be an important step in attempting to improve patient survival. The benefits (Table 6-1) of early use of phosphate binders in conjunction with improved assessment of bone turnover, PTH levels and active vitamin D therapy can yield improvements in patient overall health and survival. The overall risks of early therapy are very small being predominantly related to mild and transient GI disturbances common to all phosphate binders (nausea, vomiting, diarrhea and constipation). Hypophosphatemia as a consequence of binder use is rare and usually a result of inadequate nutrition which results in a low phosphate intake (NKF, 2002, *Am J Kidney Dis*). Drug-drug interactions are few and usually of the type associated with adsorption to the binder. These interactions are the same as those observed with over-the-counter antacids. The above risks are easily mitigated and will not contribute to safety issues if patients receive regular physician care. Current phosphate binders share characteristics of antacids and ion
exchange resins, which have been approved for use since the 1970s and have not been associated with significant risks. Current phosphate binders have been extensively studied in the CKD population on dialysis and specific risks are presented in the individual product labeling for the three products (PhosLo, Renagel, and Fosrenol, see Sections 9.1, 9.2, and 9.3). The overall risks of phosphate binder therapy for patients with CKD not on dialysis are the same as for patients on dialysis.

6.3 Benefits of Early Treatment of Hyperphosphatemia

CKD is a major public health issue whose prevalence is increasing. The consequences of CKD include significant morbidities (dialysis, cardiovascular and bone disease) as well as mortality. An important component in the genesis of these consequences are disturbances in mineral and bone metabolism (Eknoyan, Lameire, 2004, Kidney Int). Recent research is beginning to unravel the relationships between the biochemical abnormalities (calcium, phosphate, PTH and active vitamin D), bone metabolic disturbances and cardiovascular effects (vascular calcification). This broad clinical syndrome is now called CKD-Mineral and Bone Disorder (CKD-MBD) (Moe, Drueke, 2006, Kidney Int). The syndrome is manifest by abnormal biochemical parameters, bone and mineral metabolism alterations and/or extraskeletal calcifications.

CKD-MBD starts early in the course of progressive kidney failure and can modify the traditional risk factors associated with cardiovascular (Sarnak, Levey, 2003, Circulation) and bone disorders (Moe, 2006, Eur J Clin Invest). While the molecular mechanisms of mineral, bone and vascular abnormalities in CKD are now starting to be understood, there are associations between abnormal plasma levels of phosphate and the presence and extent of vascular calcification in dialysis patients (Block, Raggi, 2007, Kidney Int). These abnormal biochemical parameters may be associated with increased cardiovascular morbidity and mortality in ESRD patients on dialysis (Blacher, Guerin, 2001, Hypertension) as well as in earlier stages of CKD (Kestenbaum, Sampson, 2005, J Am Soc Nephrol; Schwarz, Trivedi, 2006, Clin J Am Soc Nephrol). Controlling abnormal laboratory parameters such as calcium, phosphate and PTH as well as preventing, slowing, or halting the progression of extraskeletal calcifications is considered a major component for prevention of the bone disease and other related morbidities and hopefully mortality in CKD patients (Moe, Drueke, 2006, Kidney Int; Moe, 2004, Semin Nephrol).

Because of the interrelationships between calcium, vitamin D, and phosphate, pharmacotherapy of these laboratory parameters is complex. Currently, there are 3 vitamin D analogs approved for the treatment of secondary hyperparathyroidism in CKD
(paracalcitol, calcitriol and doxercalciferol) both for pre-dialysis and dialysis patients. The safety and effectiveness of these agents were demonstrated in placebo controlled randomized clinical trials of up to six months duration where the endpoint was PTH levels at the end of treatment. Vitamin D supplements and derivatives can be associated with oversuppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia and adynamic bone disease. Additionally overdoses of vitamin D or its derivatives may require emergency attention if acute hypercalcemia occurs. Acute hypercalcemia may exacerbate a tendency for cardiac arrhythmia or seizures and may potentiate the action of digitalis (Abbott, 2005). The risks associated with the use of vitamin D derivatives in CKD are greater than those associated with the chronic use of phosphate binders which do not have these associated conditions.

Currently phosphate binders are indicated for the control of hyperphosphatemia in patients on dialysis. This indication is based on results of randomized clinical trials conducted in this group of patients. Three phosphate binders are currently marketed for the treatment of hyperphosphatemia in patients on dialysis.

However, by the time dialysis therapy is initiated, pathophysiological abnormalities in the calcium-phosphate-PTH-vitamin D axis have been present for many years (Orlando, Owen, 2007, \textit{N C Med J}). At the time dialysis is initiated, there are substantial abnormalities present in bone, cardiovascular system, brain and other organs. The goal of rational therapy for CKD would be to prevent as much as possible (1) the progression of kidney failure; (2) the abnormalities associated with CKD-MBD and (3) the morbidity and mortality associates with CKD progression. Because the biochemical abnormalities reflecting disorders in phosphate metabolism are evident as the GFR drops below 60 \text{mL/min/1.73m}^2 (Kestenbaum, Sampson, 2005, \textit{J Am Soc Nephrol}), the duration of therapy with phosphate binders and other therapeutic agents may be for extended periods of time before dialysis therapy is needed. Thus, it is important to consider the benefits and risks of such therapy.

The clinical status of patients with CKD starting dialysis is dependent on many factors including the nature of the underlying disease causing the CKD as well as the complications resulting from the loss of GFR (Section 3.4). CKD related conditions include obesity, diabetes, hypertension and cardiovascular diseases. CKD specific conditions include anemia due to lack of erythropoietin, fluid and electrolyte disturbances which may complicate hypertension and congestive heart failure as well as bone and mineral metabolic disturbances (calcium, phosphate, PTH, and vitamin D).

The impact of pre-dialysis care has not been prospectively investigated for any therapy. However, early referral is associated with improved prognosis and survival (Johnson,
Retrospective studies of erythropoietin use have demonstrated a reduction in mortality after initiation of dialysis (Johnson, Leopold, 2006, Circ Res). Studies of patients referred for early nephrology care compared for late nephrology care have indicated that laboratory parameters reflecting CKD-MBD are poorly controlled. A study from Japan (Nakamura, Nakata, 2007, Circ J) retrospectively studied the clinical characteristics of patients with CKD who initiated dialysis in one large referral center between the years 1983 and 2003. The characteristics of patients who entered dialysis after early (>6 months) or late (≤6 months) referral to a nephrologist for evaluation and treatment are presented in Table 6-2. Despite high use of antihypertensive medications and diuretics, systolic hypertension and increased left ventricular mass index (LVMI) was common. Few patients received vitamin D analogs or phosphate binder therapy prior to starting dialysis. Plasma calcium was at the lower end of normal and phosphate was elevated regardless of time of referral to nephrology care. During a follow-up period averaging 41 months after initiation of dialysis, 167 of 366 patients died. Analysis of survival curves demonstrated that early referral to nephrology care and age at first dialysis was statistically significantly associated with improved survival at one year and all cause mortality over the follow up period. This study was conducted in Japan; however, the patient characteristics and medication usage in CKD and dialysis are not different from those in the US or EU. The use of vitamin D analogs and phosphate binders was very low in both patient groups, however other parameters of CKD-MBD (alkaline phosphatase, calcitriol or PTH) were not reported.
Table 6-2  Selected Characteristics of Patients with CKD Who Progressed to Dialysis at Dialysis Initiation

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>All Patients (n=366)</th>
<th>Late Referral (n=172)</th>
<th>Early Referral (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid Conditions</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>98</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>60</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>30</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>11</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Aortic Aneurysm</td>
<td>15</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Smoking</td>
<td>64</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Laboratory Parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.2±1.5</td>
<td>8.1±1.6</td>
<td>8.3±1.5</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>6.3±2.1</td>
<td>6.2±2.3</td>
<td>6.4±1.9</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.2±1.0</td>
<td>8.1±0.9</td>
<td>8.2±1.1</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>192±61</td>
<td>202±64</td>
<td>184±58</td>
</tr>
<tr>
<td>Parameters Prior to First Dialysis Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-ESRD Phosphate Binders</td>
<td>36%</td>
<td>16%</td>
<td>50%</td>
</tr>
<tr>
<td>Pre ESRD Vit D</td>
<td>7%</td>
<td>3%</td>
<td>18%</td>
</tr>
<tr>
<td>Pre ESRD Erythropoietin</td>
<td>25%</td>
<td>9%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Reference: (Nakamura, Nakata, 2007, Circ J)

The results of this study and others suggest that optimal management of patients with CKD should incorporate attention to the CKD-specific risk factors of hypertension, anemia correction and early referral to specialist care. While the study draws no conclusions regarding therapy of CKD-MBD laboratory abnormalities, vitamin D has been associated with improved survival on dialysis and has been recommended to be started in CKD Stage 3 to prevent parathyroid gland hyperplasia and control PTH levels (Andress, 2006, Kidney Int). Vitamin D analogs in addition to increasing calcium absorption from the GI tract also increase phosphate absorption and may contribute to the body burden of phosphate in CKD Stage 3. Therefore, the rational approach to the therapy of CKD should include attention to kidney specific risk factors (fluid balance, anemia and CKD-MBD parameters) as well as other related risk factors (obesity, diabetes, cardiovascular disease and hypertension).

6.4 Potential Benefits of Therapy of Hyperphosphatemia in CKD Prior to Dialysis Initiation

The early and sustained reduction of phosphate available for absorption from the GI tract in CKD Stage 3-4 patients with hyperphosphatemia in conjunction with repletion of active vitamin D and appropriate dietary management to provide adequate protein intake to avoid malnutrition will provide beneficial effects in patients with CKD-MBD on bone and cardiovascular health.
6.4.1 **Adjunctive Therapy for Reduction of PTH Levels**

Low plasma calcium and high plasma phosphate levels independently stimulate release of PTH by the parathyroid gland. CKD results in progressive loss of 1-hydroxylase activity resulting in decreased levels of active vitamin D. The loss of this active vitamin results in a decrease in calcium absorption from the GI tract and increased PTH to mobilize calcium stores from bone. It is the increased demand for the kidney to excrete more phosphorus per remaining nephron that demands higher phosphatonin levels which results in lower 1,25-OH 2 D and secondary hyperparathyroidism. This mechanism serves to maintain plasma phosphate levels at normal levels until the GFR falls below 40 mL/min/1.73m². At this time dietary intake of phosphate, mobilization from bone and a reduced ability to remove excessive phosphate by filtration at the glomerulus results in hyperphosphatemia. Replacement of vitamin D to insure adequate bone remodeling and mineralization will increase calcium and phosphate absorption from the GI tract and result in decreased PTH levels. Reduction of phosphate absorption by phosphate binders will also lead to lower plasma phosphate levels and remove another direct stimulus for PTH secretion. Prolonged hypersecretion of PTH can result in parathyroid gland hypertrophy and ultimately autonomous production of PTH (tertiary hyperparathyroidism) necessitating surgical removal. Prolonged effects of PTH on bone results in renal osteodystrophy (hyperparathyroidism bone disease [HPTH or Osteitis Fibrosa cystica]). This is characterized by excessive bone resorption and high bone turnover. Prior to the availability of active vitamin D analogs, HPTH resulted in extreme bone fragility and pathologic fractures, bone marrow fibrosis, and severe refractory anemia.

6.4.2 **Reduction of Extraskeletal Calcification Associated with Uremia**

6.4.2.1 **Calciphylaxis**

Calciphylaxis or calcific uremic arteriopathy (CUA) is a fatal disease in dialysis patients due to calcification of cutaneous blood vessels (Ahmed, O'Neill, 2001, *Am J Kidney Dis*). The pathogenesis has been attributed to elevated parathyroid hormone (PTH). However, recent studies evaluating vascular calcification in non-dialysis patients have found that the smooth muscle cells play an active role as outlined in Section 4.2.4.1. Histology reveals arterial medial calcification with intimal proliferation involving small vessels in the subcutaneous fat, associated with a lymphohistiocytic infiltrate of the affected lobules. An analysis of risk factors revealed a 3.5-fold increase in the risk of calciphylaxis associated with each mg/dL increase in the mean serum phosphorus during the year prior to diagnosis (Mazhar, Johnson, 2001, *Kidney Int*). Most patients have hyperparathyroidism and an elevated Ca x P product, which is believed to be a major causative factor. The therapeutic strategy is to normalize the
high Ca × P products. When severe hyperparathyroidism (HPT) is present, parathyroidectomy (PTX) should be performed. However, for patients with low PTH level, calciphylaxis is unresponsive to PTX, and such an approach may worsen hyperphosphatemia and hypercalcemia. In these cases aggressive treatment with non-calcium based phosphate binders and changes in vitamin D therapy are the only possibilities. The mortality rate of 80% in the first year is very high. While observed primarily in patients on dialysis with high Ca × P product, the pathogenesis is believed to be related to prolonged exposure to high calcium and phosphate levels in plasma. Nowadays, calciphylaxis occurs more frequently in association with adynamic (low turnover) bone disease (Mawad, Sawaya, 1999, *Clin Nephrol*). Therapy with phosphate binders to maintain control of plasma phosphate and Ca × P product is indicated to avoid precipitating this fatal condition.

### 6.4.2.2 Vascular Calcification

Cardiovascular disease is common with ESRD and accounts for at least 50% of deaths among these patients. Vascular calcifications are implicated as a possible cause of this cardiovascular mortality (Negri, 2005, *Curr Vasc Pharmacol*). The striking feature of uremic vascular disease is medial calcification. Evidence suggests that vascular calcification is an active and highly regulated process similar to bone formation (Hruska, Saab, 2007, *Semin Dial*). Elevated levels of phosphorus and/or other uremic toxins may also play an important role by inducing the transformation of vascular smooth muscle cells into osteoblast-like cells, which can produce bone matrix proteins (Cozzolino, Gallieni, 2006, *Semin Nephrol*; Mathew, Davies, 2006, *Eur J Clin Invest*). This process is mediated by phosphate as the signal through the PIT-1 transporter to initiate a cascade of events culminating in mineralization (El-Abbadi and Giachelli, 2007, *Adv Chronic Kidney Dis*). The advent of newer noninvasive screening tests has generated great interest in screening patients with CKD and ESRD for vascular calcifications.

The detection, prevention, and treatment of vascular calcification in CKD patients are critical for the overall approach to the management of these patients. Hyperphosphatemia, especially when the blood levels of serum phosphorus are above 5.5 mg/dl, plays a major role in the development of vascular calcification. With a high Ca × P product, hyperphosphatemia drives the direct deposition of calcium salts in arteries and cardiac valves. The active process involves the uptake of phosphate by the vascular smooth muscle cells via the PIT-1 transporter. The increase in cell phosphate then induces an osteoblastic transformation, which in turn, results in extracellular mineralization. In a study of patients new to dialysis, baseline CAC score, as measured by electron-beam computed tomography, is an independent
predictor of mortality in (CAC=0; CAC 1-400; CAC ≥400). This trial confirms the finding that severity of CAC at the time of initiation of hemodialysis is an important predictor of long-term survival (Block, Raggi, 2007, *Kidney Int*). Therefore, it is critical that the blood levels of serum phosphorus be maintained below 5.5 mg/dl in CKD patients on dialysis.

A number of studies have attempted to investigate the effects of phosphate binders on CAC in patients on dialysis. These have been reviewed by Kestenbaum (Kestenbaum, 2007, *Semin Dial*). Because of the severity and risk of calciphylaxis in patients on dialysis, it is not possible to test the effects of phosphate binder compared to placebo in a randomized controlled trial.

A similar situation exists for mortality studies in dialysis patients. There have been few clinical studies examining the effect of phosphate binders on cardiovascular outcomes and mortality. However, most of the observational studies in dialysis patients show a strong association of hyperphosphatemia with mortality (Kestenbaum, 2007, *Semin Dial*). There have been a number of other mortality outcome trials in patients with CKD both pre and on dialysis that have either not met their primary endpoints or were discontinued prematurely. These include two dialysis dose trials (HEMO and ADEMEX); Atorvastatin and Fluvastatin therapy to lower LDL cholesterol (4-D, Fluvastatin trial); Erythropoietin (US Normal Hematocrit trial, CHOIR and CREATE); and a folic acid trial to lower homocysteine. One must ask why so many failed trials in this population. One possible explanation is that CKD introduces a new set of risk factors that are additive to those already present. The majority of failed trials are in patients on dialysis therapy. This may suggest that dialysis is associated with its own set of risks that cannot be modifiable at this stage of disease. The complexity of CKD associated and CKD related risk factors may preclude meaningful results from single effect interventions if other factors cannot be controlled.

**6.4.2.3 Effects on Bone**

Phosphate retention is known to play a role in the development of renal osteodystrophy (Lund, Davies, 2006, *J Bone Miner Metab*). Bone histomorphometric studies have examined the effects of phosphate binder treatment on the evolution of renal osteodystrophy (Freemont, Hoyland, 2005, *Clin Nephrol*; Salusky, Goodman, 2005, *J Am Soc Nephrol*). These studies have been of critical importance, because the use of aluminum hydroxide in the 1970’s as a potent cheap phosphate binder for patients on dialysis and was associated with osteomalacia and aluminum deposition at the mineralization front in bone (Malluche, 2002, *Nephrol Dial Transplant*; Vick and Johnson, 1985, *Clin Pharm*). These observations of the 1970s led to the discontinuation of the widespread use of aluminum-containing antacids as
phosphate binders. Bone is a dynamic organ and is primarily involved in regulating calcium and phosphate loads. Low turnover bone disease decreases the ability of the bone to buffer phosphate and has been associated directly with increased vascular calcification (London, Marty, 2004, *J Am Soc Nephrol*).

### 6.4.2.4 Effects on Progression of Kidney Disease

In CKD, the progression of renal dysfunction can be mediated by a multitude of factors including the cause of CKD, hyperphosphatemia, hyperparathyroidism, lack of active vitamin D, and possibly excess of the phosphaturic hormone FGF-23. Early experimental work suggested a beneficial role of phosphate restriction on progression in rats with nephrotoxic nephritis and 5/6 nephrectomy remnant kidney models which was PTH independent (Ritz, Gross, 2005, *Kidney Int Suppl*). Observational studies suggested an association between phosphate and progressive decline of GFR in humans (Barrientos, Arteaga, 1982, *Miner Electrolyte Metab*; Ihle, Becker, 1989, *N Engl J Med*; Levey, Greene, 2006, *Am J Kidney Dis*; Maschio, OldrizzI, 1982, *Kidney Int*; NKF, 2003, *Am J Kidney Dis*; Torres, Prie, 2007, *Kidney Int* in humans. However, not all studies observed the same effect (Williams, Stevens, 1991, *Q J Med*). The complex relationships in human studies between dietary interventions, active vitamin D replacement phosphate binders and PTH levels complicate standardizing study design to evaluate the effects of single interventions. Recent evidence in animals suggests that mutations in the KLOTHO gene can produce a syndrome resembling ageing and CKD and that phosphate restriction can mitigate these effects (Torres, Prie, 2007, *Kidney Int*). While these results are not yet conclusive the evidence accumulated over the last 20 years suggests that appropriate management of CKD to retard decline in GFR needs to involve limitation of phosphate intake but provision of adequate dietary protein to avoid malnutrition. A phosphate intake of 750 mg/day corresponds to a protein intake of approximately 50 gm/day. Thus to maintain protein intake of approximately 1 gm/kg/day, phosphate binders may be required to avoid phosphate imbalance. This is especially important if active vitamin D is also administered which results in increased phosphate reabsorption (Cupisti, Morelli, 2003, *J Nephrol*).

### 6.5 Risks of Phosphate Binder Therapy

#### 6.5.1 GI Events and Hypophosphatemia

The risks of phosphate binder therapy with currently approved products have been extensively studied. There are two main categories of risk: short term and long term. The short term AEs associated with all three marketed products are related to the GI tract. The main AE are nausea, vomiting, constipation and/or diarrhea. These events are transient and
abate with continued dosing and require very few discontinuations when the products are taken as directed. Importantly, they are the same events as reported in patients taking over-the-counter antacids for the treatment of GI disorders as well as for phosphate binders.

There is only one long term AE that may occur with extended use of phosphate binders in CKD and that is hypophosphatemia with phosphate depletion syndrome. The phosphate depletion syndrome as a consequence of phosphate binders in CKD was sporadically reported in the 1960s and 70s in association with antacid treatment of hyperphosphatemia (Berner and Shike, 1988, Annu Rev Nutr; NKF, 2003, Am J Kidney Dis). While total doses of phosphate binders were not reported, some of the patients had taken up to 75 tablets of Mylanta (Aluminum Hydroxide, 200mg [Antacid], Magnesium Hydroxide, 200mg [Antacid], Simethicone, 20 mg [Antigas]) daily. In a controlled setting, phosphate depletion in patients with CKD can be induced by administration of a molar excess of aluminum carbonate gel ($\text{Al}_2(\text{CO}_3)_3$: 4000 mg orally 4 times daily) while limiting phosphate intake to 650 mg a day. The time required to reduce phosphate levels in patients with CKD under these conditions varied from 2 to 12 days (NKF, 2002, Am J Kidney Dis). It must be noted that this dose of phosphate binder is in great excess relative to doses of all the approved phosphate binders currently on the market. Cases of phosphate depletion in patients with or without CKD continue to be rare since proton pump inhibitors and histamine receptor antagonists have replaced high dose antacids in the treatment of peptic ulcer disease.

Patients with CKD under adequate physician care should have serum laboratory evaluations including calcium, phosphorus, and magnesium levels monitored periodically. If nutritional intake is adequate, it would take many years of continued therapy to see clinical symptoms of phosphate depletion.

Therapy for phosphate depletion syndrome is dependent on the severity of the depletion. Mild hypophosphatemia with plasma phosphate levels above 2 mg/dL requires no treatment except withholding phosphate binders until the phosphate increases to the desired target. Moderate phosphate depletion with levels between 1 and 2 mg/dL can also be treated in a similar fashion but may require an increase in protein in the diet in addition to withholding binders. Severe phosphate depletion with plasma phosphate levels less than 0.5 mg/dl will require replacement with oral phosphate over a period of 1 to 2 weeks. A summary of the phosphate depletion syndrome, its causes and therapy is presented in the review by Berner (Berner and Shike, 1988, Annu Rev Nutr).
6.5.2 Drug-Drug Interactions

Patients with chronic illness such as CKD require long-term treatment with many different agents. This increases the possibility for drug-drug interactions. The three agents approved as phosphate binders are either related to the antacids or to ion exchange resins.

Antacid-type drug interactions are primarily due to interference with drug absorption due by the phosphate binder. The majority of these types of interactions can be overcome by staggering administration of drug and phosphate binder. A similar strategy is also employed with ion-exchange resins to avoid complex formation with co-administered drugs.

One other rare risk associated with certain metal-based phosphate binders is the formation of renal calculi. These calculi may be the consequence of metabolic effects or absorption of cations that depend on the kidney for excretion. Calcium-, magnesium-, and aluminum-based salts have been associated with calculi but only account for around 0.1% of all drug-induced metabolic calculi. In patients with CKD, vitamin D analogs are a rare cause of calcium oxalate calculi, primarily in patients on dialysis who maintain some residual diuresis. The likely mechanism is related to the high concentration of urinary oxalate and protein in the remaining nephrons. If the filtered calcium load is increased secondary to vitamin D administration, then the solubility product of calcium and oxalate may be exceeded, and crystallization occurs in conjunction with an admixture of proteins (Daudon and Jungers, 2004, Drugs; Oreopoulos and Silverberg, 1974, N Engl J Med). The overall risk from drug-drug interactions and renal calculi is small.

6.5.3 Summary

- Phosphate binders are currently indicated for the treatment of hyperphosphatemia in patients on dialysis.

- Hyperphosphatemia and its associated pathophysiological abnormalities begin in CKD Stage 3 and become more severe as the GFR declines.

- The pathophysiology of phosphate is complex and involves components of the vitamin D, PTH, and phosphatonin systems, implicating phosphate as a signal molecule rather than a passive participant in metabolic processes.

- Evidence from translational research and clinical epidemiology supports the emerging role of hyperphosphatemia as a risk factor for the clinical features of CKD-MBD.
• Because of the multitude of processes involved with CKD-MBD, interventional trials examining a single factor may not provide definitive evidence of effects on mortality in patients with CKD.

• The overall benefits and risks long term treatment for hyperphosphatemia deserve careful consideration.
  - Hyperphosphatemia is associated with increased morbidity and mortality both in patients with CKD on dialysis and not on dialysis.
  - Attenuating the progression of renal disease by reducing GI availability and absorption of phosphate is one component of the rational treatment of CKD-MBD.
  - Starting in CKD Stage 3, active vitamin D is needed to assure adequate bone formation and mineralization. Active vitamin D analogs have been approved for use in CKD Stages 3 through 5 for control of secondary hyperparathyroidism.
  - The use of phosphate binders in CKD when phosphate balance becomes positive will benefit patients by controlling PTH levels, delaying the progression of renal osteodystrophy and reducing progression of vascular calcification in those patients who are predisposed.
  - The overall risks of treatment even for long periods are minimal if the patients receive regular medical attention and laboratory follow up.
  - The primary short-term risks are AEs associated with GI tract disturbances which are mild and transient.
  - Hypophosphatemia in patients receiving adequate nutrition and protein intake is rare. In the few patients who develop phosphate depletion, treatment is well defined and requires low resources (improving nutrition and decreasing phosphate binder dose).
  - The risks of phosphate binder use in patients hyperphosphatemic CKD patients not on dialysis are not different from patients with CKD on dialysis.
  - Overall the benefit-risk balance of phosphate binders in patients with CKD is positive in favor of treatment and minimal in terms of risk.
7. CONCLUSIONS

As discussed, hyperphosphatemia is a key component in CKD-Metabolic Bone Disorder. Hyperphosphatemia presents well before CKD has progressed to the point at which renal replacement therapy is required and is an independent risk factor for cardiovascular morbidity and mortality. Current KDOQI guidelines recommend early detection and intervention in the treatment of elevated serum phosphorus in patients with CKD. Given this guidance, the understanding that CKD progresses as a continuum, and considerable evidence of benefit and limited risks to treat CKD patients with phosphate binder therapy, it is the position of all companies invited to participate in this FDA advisory committee that no distinction be made in treatment of hyperphosphatemia in CKD patients based on dialysis status. All three companies believe that the current evidence is sufficient to support expanding the current indication for phosphate binders to control of hyperphosphatemia in CKD patients prior to and following the initiation of dialysis.
8. REFERENCES


Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16(2):434-44. [Provided upon request]


USRDS. 2006 USRDS Annual Data Report. Minneapolis, MN: Coordinating Center, Minneapolis Medical Research Foundation; funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in conjunction with the Centers for Medicare & Medicaid Services; 2006.


9. APPENDICES

9.1 PhosLo Package Insert (Fresenius Medical Care North America)
PhosLo® Gelcaps (Calcium Acetate) R® only

DESCRIPTION: Each opaque gelcap with a blue cap and white body is spin printed in blue and white ink with “PhosLo®” printed on the cap and “667 mg” printed on the body. Each gelcap contains 667 mg calcium acetate, USP (anhydrous; Ca(CH3COO)2; MW=158.17 grams) equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000 NF. The gelatin cap and body have the following inactive ingredients: FD&C blue #1, D&C red #28, titanium dioxide, USP and gelatin, USP.

PhosLo® Gelcaps (calcium acetate) are administered orally for the control of hyperphosphatemia in end-stage renal failure.

CLINICAL PHARMACOLOGY: Patients with advanced renal insufficiency (creatinine clearance less than 30 ml/min) exhibit phosphate retention and some degree of hyperphosphatemia. The retention of phosphate plays a pivotal role in causing secondary hyperparathyroidism associated with osteodystrophy, and soft-tissue calcification. Therapy by itself will not normalize phosphate retention in hyperparathyroidism is not clearly delineated. Therapeutic efforts directed toward the control of hyperphosphatemia include reduction in the dietary intake of phosphate, inhibition of absorption of phosphate in the intestine with phosphate binders, and removal of phosphate from the body by more efficient methods of dialysis. The rate of removal of phosphate by dietary manipulation or by dialysis is insufficient. Dialysis patients absorb 40% to 50% of dietary phosphorus. Therefore, the fraction of dietary phosphate absorbed from the diet needs to be reduced by using phosphate binders in most renal failure patients on maintenance dialysis. Calcium acetate (PhosLo®) when taken with meals, combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Maintenance of serum phosphorus below 6.0 mg/dl is generally considered as a clinically acceptable outcome of treatment with phosphate binders. PhosLo is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine.

Orally administered calcium acetate from pharmaceutical dosage forms has been demonstrated to be systemically absorbed up to approximately 40% under fasting conditions and up to approximately 30% under non-fasting conditions. This range represents data from both healthy subjects and renal dialysis patients under various conditions.

INDICATIONS AND USAGE: PhosLo® is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS: Patients with end stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently with PhosLo®. Progressive hypercalcemia due to overdose of PhosLo® may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period. The serum calcium times phosphate (CaXP) product should not be allowed to exceed 66. Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft tissue calcification.

PRECAUTIONS: GENERAL: Excessive dosage of PhosLo® induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. PhosLo® should not be given to patients on digitals, because hypercalcemia may precipitate cardiac arrhythmias. PhosLo® therapy should always be started at low dose and should not be increased without careful monitoring of serum calcium. An estimate of daily calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically.

Information for the Patient: The patient should be informed about compliance with dosage instructions, adherence to instructions about diet and avoidance of the use of nonprescription antacids. Patients should be informed about the symptoms of hypercalcemia (see ADVERSE REACTIONS section).

Drug Interactions: PhosLo® may decrease the bioavailability of tetracyclines.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term animal studies have not been performed to evaluate the carcinogenic potential, mutagenicity, or effect on fertility of PhosLo®.

Pregnancy: Teratogenic Effects: Category C. Animal reproduction studies have not been conducted with PhosLo®. It is not known whether PhosLo® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PhosLo® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of subjects in clinical studies of PhosLo® (n=91), 25 percent were 65 and over, while 7 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: In clinical studies, patients have occasionally experienced nausea during PhosLo® therapy. Hypercalcemia may occur during treatment with PhosLo®. Mild hypercalcemia (Ca>10.5mg/dl) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia (Ca>12mg/dl) is associated with confusion, delirium, stupor and coma. Mild hypercalcemia is easily controlled by reducing the PhosLo® dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo® therapy. Decreasing dialysate calcium concentration could reduce the incidence and severity of PhosLo®-induced hypercalcemia. The long-term effect of PhosLo® on the progression of vascular or soft tissue calcification has not been determined. Isolated cases of pruritus have been reported which may represent allergic reactions.

OVERDOSE: Administration of PhosLo® in excess of the appropriate daily dosage can cause severe hypercalcemia (see ADVERSE REACTIONS section).

DOSAGE AND ADMINISTRATION: The recommended initial dose of PhosLo® for the adult dialysis patient is 2 gelcaps with each meal. The dosage may be increased gradually to bring the serum phosphate value below 6 mg/dl, as long as hypercalcemia does not develop. Most patients require 3-4 gelcaps with each meal.

HOW SUPPLIED: Gelcap: A white and blue gelcap for oral administration containing 667 mg calcium acetate (anhydrous Ca(CH3COO)2; MW=158.17 grams) equal to 169 mg (8.45 mEq) calcium. Gelcap NDC 4920-640-21 Bottles of 200

STORAGE: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). See USP “Controlled Room Temperature.”

Manufactured for Fresenius Medical Care North America Waltham, MA 02451 1-800-323-5188

100647-01 01/2007
9.2 Fosrenol Package Insert (Shire US)
FOSRENOL® (foss-wren-all)
(Lanthanum Carbonate) 500, 750, and 1000 mg Chewable Tablets.

DESCRIPTION

FOSRENOL® contains lanthanum carbonate (2:3) hydrate with molecular formula La₂(CO₃)₃
xH₂O (on average x=4-5 moles of water) and molecular weight 457.8 (anhydrous mass).
Lanthanum (La) is a naturally occurring rare earth element. Lanthanum carbonate is
practically insoluble in water.
Each FOSRENOL®, white to off-white, chewable tablet contains lanthanum carbonate
hydrate equivalent to 500, 750, or 1000 mg of elemental lanthanum and the following inactive
ingredients: dextrates (hydrated) NF, colloidal silicon dioxide NF, magnesium stearate NF.

CLINICAL PHARMACOLOGY

Patients with end stage renal disease (ESRD) can develop hyperphosphatemia that may be
associated with secondary hyperparathyroidism and elevated calcium phosphate product.
Elevated calcium phosphate product increases the risk of ectopic calcification. Treatment of
hyperphosphatemia usually includes all of the following: reduction in dietary intake of
phosphate, removal of phosphate by dialysis and inhibition of intestinal phosphate absorption
with phosphate binders. FOSRENOL® does not contain calcium or aluminum.

Pharmacodynamics:
Lanthanum carbonate dissociates in the acid environment of the upper GI tract to release
lanthanum ions that bind dietary phosphate released from food during digestion.
FOSRENOL® inhibits absorption of phosphate by forming highly insoluble lanthanum
phosphate complexes, consequently reducing both serum phosphate and calcium phosphate product.

*In vitro* studies have shown that in the physiologically relevant pH range of 3 to 5 in gastric fluid, lanthanum binds approximately 97% of the available phosphate when lanthanum is present in a two-fold molar excess to phosphate. In order to bind dietary phosphate efficiently, lanthanum should be administered with or immediately after a meal.

**Pharmacokinetics:**

**Absorption/Distribution:**

Following single or multiple dose oral administration of FOSRENOL® to healthy subjects, the concentration of lanthanum in plasma was very low (bioavailability <0.002%). Following oral administration in ESRD patients, the mean lanthanum C\(_{\text{max}}\) was 1.0 ng/mL. During long-term administration (52 weeks) in ESRD patients, the mean lanthanum concentration in plasma was approximately 0.6 ng/mL. There was minimal increase in plasma lanthanum concentrations with increasing doses within the therapeutic dose range. The effect of food on the bioavailability of FOSRENOL® has not been evaluated, but the timing of food intake relative to lanthanum administration (during and 30 minutes after food intake) has a negligible effect on the systemic level of lanthanum.

*In vitro*, lanthanum is highly bound (>99%) to human plasma proteins, including human serum albumin, α1-acid glycoprotein, and transferrin. Binding to erythrocytes *in vivo* is negligible in rats.

In 105 bone biopsies from patients treated with FOSRENOL® for up to 4.5 years, rising levels of lanthanum were noted over time. Estimates of elimination half-life from bone
ranged from 2.0 to 3.6 years. Steady state bone concentrations were not reached during the
period studied.

In studies in mice, rats and dogs, lanthanum concentrations in many tissues increased over
time and were several orders of magnitude higher than plasma concentrations (particularly in
the GI tract, bone and liver). Steady state tissue concentrations in bone and liver were
achieved in dogs between 4 and 26 weeks. Relatively high levels of lanthanum remained in
these tissues for longer than 6 months after cessation of dosing in dogs. There is no
evidence from animal studies that lanthanum crosses the blood-brain barrier.

Metabolism/Elimination:

Lanthanum is not metabolized and is not a substrate of CYP450. In vitro metabolic inhibition
studies showed that lanthanum at concentrations of 10 and 40 µg/ml does not have relevant
inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, and
3A4/5). Lanthanum was cleared from plasma following discontinuation of therapy with an
elimination half-life 53 hours.

No information is available regarding the mass balance of lanthanum in humans after oral
administration. In rats and dogs, the mean recovery of lanthanum after an oral dose was
about 99% and 94% respectively and was essentially all from feces. Biliary excretion is the
predominant route of elimination for circulating lanthanum in rats. In healthy volunteers
administered intravenous lanthanum as the soluble chloride salt (120 µg), renal clearance
was less than 2% of total plasma clearance. Quantifiable amounts of lanthanum were not
measured in the dialysate of treated ESRD patients.

In Vitro- Drug Interactions:
Gastric Fluid: The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, and enalapril) was investigated in simulated gastric fluid. The results suggest that precipitation in the stomach of insoluble complexes of these drugs with lanthanum is unlikely.

In Vivo- Drug Interactions:
Lanthanum carbonate is neither a substrate nor an inhibitor of CYP450 enzymes. The absorption of a single dose of 1000 mg of FOSRENOL® is unaffected by co-administration of citrate. No effects of lanthanum were found on the absorption of digoxin (0.5-mg), metoprolol (100-mg), or warfarin (10-mg) in healthy subjects co-administered lanthanum carbonate (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g., bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies were done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

Clinical Trials:
The effectiveness of FOSRENOL® in reducing serum phosphorus in ESRD patients was demonstrated in one short-term, placebo-controlled, double-blind dose-ranging study, two placebo-controlled randomized withdrawal studies and two long-term, active-controlled, open-label studies in both hemodialysis and peritoneal dialysis (PD) patients.

Double-Blind Placebo-Controlled Studies:
One hundred forty-four patients with chronic renal failure undergoing hemodialysis and with elevated phosphate levels were randomized to double-blind treatment at a fixed dose of
lanthanum carbonate of 225 mg (n=27), 675 mg (n=29), 1350 mg (n=30) or 2250 mg (n=26) or placebo (n=32) in divided doses with meals. Fifty-five percent of subjects were male, 71% black, 25% white and 4% of other races. The mean age was 56 years and the duration of dialysis ranged from 0.5 to 15.3 years. Steady-state effects were achieved after two weeks. The effect after six weeks of treatment is shown in Figure 1.

**Figure 1. Difference in Phosphate Reduction in the FOSRENOL® and Placebo Group in a 6-Week, Dose-Ranging, Double-Blind Study in ESRD Patients (with 95% Confidence Intervals)**

One-hundred eighty five patients with end-stage renal disease undergoing either hemodialysis (n=146) or peritoneal dialysis (n=39) were enrolled in two placebo-controlled, randomized withdrawal studies. Sixty-four percent of subjects were male, 28% black, 62%
white and 10% of other races. The mean age was 58.4 years and the duration of dialysis ranged from 0.2 to 21.4 years. After titration of lanthanum carbonate to achieve a phosphate level between 4.2 and 5.6 mg/dL in one study (doses up to 2250 mg/day) or ≤ 5.9 mg/dL in the second study (doses up to 3000 mg/day) and maintenance through 6 weeks, patients were randomized to lanthanum or placebo. During the placebo-controlled, randomized withdrawal phase (four weeks), the phosphorus concentration rose in the placebo group by 1.9 mg/dL in both studies relative to patients who remained on lanthanum carbonate therapy.

**Open-Label Active-Controlled Studies:**

Two long-term open-label studies were conducted, involving a total of 2028 patients with ESRD undergoing hemodialysis. Patients were randomized to receive FOSRENOL® or alternative phosphate binders for up to six months in one study and two years in the other. The daily FOSRENOL® doses, divided and taken with meals, ranged from 375 mg to 3000 mg. Doses were titrated to reduce serum phosphate levels to a target level. The daily doses of the alternative therapy were based on current prescribing information or those commonly utilized. Both treatment groups had similar reductions in serum phosphate of about 1.8 mg/dL. Maintenance of reduction was observed for up to three years in patients treated with FOSRENOL® in long-term, open label extensions.

No effects of FOSRENOL® on serum levels of 25-dihydroxy vitamin D3, vitamin A, vitamin B12, vitamin E and vitamin K were observed in patients who were monitored for 6 months.

Paired bone biopsies (at baseline and at one or two years) in 69 patients randomized to either FOSRENOL® or calcium carbonate in one study and 71 patients randomized to either FOSRENOL® or alternative therapy in a second study showed no differences in the development of mineralization defects between the groups.
Vital Status was known for over 2000 patients, 97% of those participating in the clinical program during and after receiving treatment. The adjusted yearly mortality rate (rate/years of observation) for patients treated with FOSRENOL® or alternative therapy was 6.6%.

INDICATIONS AND USAGE
FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease.

CONTRAINDICATIONS
None known.

PRECAUTIONS
General:
Patients with acute peptic ulcer, ulcerative colitis, Crohn’s disease or bowel obstruction were not included in FOSRENOL® clinical studies. Caution should be used in patients with these conditions.

Diagnostic Tests:
Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

Long-term Effects:
There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years.

Information for the Patient:

FOSRENOL® tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

Notify your physician that you are taking FOSRENOL® prior to an abdominal x-ray (see PRECAUTIONS, Diagnostic Tests).

Drug Interactions:

FOSRENOL® is not metabolized.

Studies in healthy subjects have shown that FOSRENOL® does not adversely affect the pharmacokinetics of warfarin, digoxin or metoprolol. The absorption and pharmacokinetics of FOSRENOL® are unaffected by co-administration with citrate-containing compounds (see CLINICAL PHARMACOLOGY: In Vitro/In Vivo Drug Interactions).

An in vitro study showed no evidence that FOSRENOL® forms insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril in simulated gastric fluid. However, it is recommended that compounds known to interact with antacids should not be taken within 2 hours of dosing with FOSRENOL®.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg of the salt per kg/day [2.5 times the maximum recommended daily human dose (MRHD) of 5725 mg, on a mg/m² basis, assuming a 60-kg patient] revealed no evidence of carcinogenic potential. In the mouse, oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.

Lanthanum carbonate tested negative for mutagenic activity in an *in vitro* Ames assay using *Salmonella typhimurium* and *Escherichia coli* strains and *in vitro* HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2000 mg/kg (1.7 times the MRHD), and in micronucleus and unscheduled DNA synthesis assays in rats given IV lanthanum chloride at doses up to 0.1 mg/kg, a dose that produced plasma lanthanum concentrations >2000 times the peak human plasma concentration.

Lanthanum carbonate, at doses up to 2000 mg/kg/day (3.4 times the MRHD), did not affect fertility or mating performance of male or female rats.

**Pregnancy:**

Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. The effect of FOSRENOL® on the absorption of vitamins and other nutrients has not been studied in pregnant women. FOSRENOL® is not recommended for use during pregnancy.

In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption,
increased post-implantation loss, reduced fetal weights, and delayed fetal ossification.

Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

**Labor and Delivery**

No lanthanum carbonate treatment-related effects on labor and delivery were seen in animal studies. The effects of lanthanum carbonate on labor and delivery in humans is unknown.

**Nursing Mothers:**

It is not known whether lanthanum carbonate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSRENOL® is administered to a nursing woman.

**Geriatric Use:**

Of the total number of patients in clinical studies of FOSRENOL®, 32% (538) were ≥ 65, while 9.3% (159) were ≥ 75. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients.

**Pediatric Use:**

While growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of FOSRENOL® in this population is not recommended.
**ADVERSE REACTIONS**

The most common adverse events for FOSRENOL® were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.

In double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to FOSRENOL® and placebo, respectively, for 4-6 weeks of treatment, the most common events that were more frequent (≥5% difference) in the FOSRENOL® group were nausea, vomiting, dialysis graft occlusion, and abdominal pain (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>FOSRENOL® % (N=180)</th>
<th>Placebo % (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Dialysis graft occlusion</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

The safety of FOSRENOL® was studied in two long-term clinical trials, which included 1215 patients treated with FOSRENOL® and 943 with alternative therapy. Fourteen percent (14%) of patients in these comparative, open-label studies discontinued in the FOSRENOL®-treated group due to adverse events. Gastrointestinal adverse events, such as nausea, diarrhea and vomiting were the most common type of event leading to discontinuation.

The most common adverse events (≥5% in either treatment group) in both the long-term (2 year), open-label, active controlled, study of FOSRENOL® vs. alternative therapy (Study A) and the 6-month, comparative study of FOSRENOL® vs. calcium carbonate (Study B) are
shown in Table 2. In Table 2, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 0.9 years on lanthanum and 1.3 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.71.

Table 2. Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B

<table>
<thead>
<tr>
<th></th>
<th>Study A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOSRENOL® (N = 682)</td>
<td>Alternative Therapy Adjusted Rates (N=676)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Dialysis graft complication</td>
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<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Dialysis graft occlusion</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>17</td>
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<td>Hypotension</td>
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<tr>
<td>Constipation</td>
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<td>Rhinitis</td>
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<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

OVERDOSAGE

There is no experience with FOSRENOL® overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg. In clinical trials, daily doses up to 4718 mg/day of lanthanum were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. Given the topical activity of lanthanum in the gut, and the
excretion in feces of the majority of the dose, supportive therapy is recommended for
overdosage.

**DOSAGE AND ADMINISTRATION**

The total daily dose of FOSRENOL® should be divided and taken with meals. The
recommended initial total daily dose of FOSRENOL® is 750-1500 mg. The dose should be
titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum
phosphate levels should be monitored as needed during dose titration and on a regular basis
thereafter.

In clinical studies of ESRD patients, FOSRENOL® doses up to 3750 mg were evaluated.
Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma
phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750
mg/day.

**Tablets should be chewed completely before swallowing. Intact tablets should not be
swallowed.**

**HOW SUPPLIED**

FOSRENOL® is supplied as a chewable, tablet in three dosage strengths for oral
administration: 500 mg tablets, 750 mg tablets, and 1000 mg tablets. Each chewable tablet
is white to off-white round, flat with a bevelled edge, and embossed on one side with ‘S405’
and the dosage strength corresponding to the content of elemental lanthanum.

500 mg Patient Pack (2 bottles of 45 tablets, NDC 54092-252-45, per each patient pack)
NDC 54092-252-90
750 mg Patient Pack (6 bottles of 15 tablets, NDC 54092-253-15, per each patient pack)
NDC 54092-253-90

1000 mg Patient Pack (9 bottles of 10 tablets, NDC 54092 254-10, per each patient pack)
NDC 54092-254-90

Storage
Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)
[See USP controlled room temperature]
Protect from moisture

Rx only
Manufactured for Shire US Inc.
Wayne, PA 19087, USA
1-800-828-2088
Patent number: US 5,968,976
Revision Date: 7/2007
251 0107 002
9.3 Renagel Package Insert (Genzyme Corporation)
Renagel® Tablets (sevelamer hydrochloride) 400 and 800 mg

DESCRIPTION
The active ingredient in Renagel® Tablets is sevelamer hydrochloride, a polymeric phosphate binder intended for oral administration. Sevelamer hydrochloride is poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which forty percent of the amines are protonated. It is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic, but insoluble in water. The structure is represented below:

![Chemical Structure of Sevelamer Hydrochloride]

- **a, b** = number of primary amine groups
- **c** = number of crosslinking groups
- **n** = fraction of protonated amines
- **m** = large number to indicate extended polymer network

The primary amine groups shown in the structure are derived directly from poly(allylamine hydrochloride). The crosslinking groups consist of two secondary amine groups derived from poly(allylamine hydrochloride) and one molecule of epichlorohydrin.

Renagel® Tablets: Each film-coated tablet of Renagel contains either 800 mg or 400 mg of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. The tablet imprint contains iron oxide black ink.

*Registered trademark of Genzyme Corporation.

CLINICAL PHARMACOLOGY
Patients with end-stage renal disease (ESRD) retain phosphorus and can develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium resulting in ectopic calcification. When the product of serum calcium and phosphorus concentrations (Ca x P) exceeds 55 mg^2/dL^2, there is an increased risk that ectopic calcification will occur. Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An increase in parathyroid hormone (PTH) levels is characteristic of patients with chronic renal failure. Increased levels of PTH can lead to osteitis fibrosa, a bone disease. A decrease in serum phosphorus may decrease serum PTH levels.

Treatment of hyperphosphatemia includes reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. Renagel taken with meals has been shown to decrease serum phosphorus concentrations in patients with ESRD who are on hemodialysis. In vitro studies have shown that the capsule and tablet formulations bind phosphate to a similar extent. Renagel does not contain aluminum or other metals and does not cause aluminum intoxication.

Renagel treatment also results in a lowering of low-density lipoprotein (LDL) and total serum cholesterol levels.

Pharmacokinetics: A mass balance study using 14C-sevelamer hydrochloride in 16 healthy male and female volunteers showed that sevelamer hydrochloride is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

Clinical trials: The ability of Renagel Capsules to lower serum phosphorus in ESRD patients on hemodialysis was demonstrated in six clinical trials: one double-blind placebo controlled 2-week study (renagel N=24); two open-label uncontrolled 8-week studies (renagel N=220) and three active-controlled open-label studies with treatment durations of 8 to 52 weeks (renagel N=256). Two of the active-controlled studies are described here. One trial is a crossover trial with two 8-week periods comparing Renagel to calcium acetate and the other trial is a 52-week parallel design trial comparing Renagel tablets with calcium acetate and calcium carbonate.

Cross-over study of Renagel Capsules and calcium acetate: Eighty-four ESRD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period were randomized to receive either Renagel Capsules for eight weeks followed by calcium acetate for eight weeks or calcium acetate for eight weeks followed by Renagel Capsules for eight weeks. Treatment periods were separated by a two-week phosphate binder washout period. Patients started on Renagel Capsules or calcium acetate tablets three times per day with meals. Over each eight-week treatment period, at three separate time points the dose of either agent could be titrated up 1 capsule or tablet per meal (3 per day) to control serum phosphorus. Renagel Capsules and calcium acetate both significantly decreased mean serum phosphorus by about 2 mg/dL (Table 1).

Table 1. Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Renagel (N=81)</th>
<th>Calcium (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline at End of Washout</td>
<td>8.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Change from Baseline at Endpoint (95% Confidence Interval)</td>
<td>-2.0* (-2.5, -1.5)</td>
<td>-2.1* (-2.6, -1.7)</td>
</tr>
</tbody>
</table>

*p < 0.0001, within treatment group comparison

Figure 1 illustrates that the proportion of patients achieving a given level of serum phosphorus lowering is comparable between the two treatment groups. For example, about half the patients in each group had a decrease of at least 2 mg/dL at endpoint.

Renagel® Tablets (sevelamer hydrochloride)
**Renagel® Tablets**  
(sevelamer hydrochloride)

### Indications and Usage

Renagel is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on hemodialysis. The safety and efficacy of Renagel in patients who are not on hemodialysis have not been studied. In hemodialysis patients, Renagel decreases the incidence of hypercalcemic episodes relative to patients on calcium treatment.

### Contraindications

Renagel is contraindicated in patients with hypophosphatemia or bowel obstruction. Renagel is contraindicated in patients known to be hypersensitive to sevelamer hydrochloride or any of its constituents.

### Precautions

**General:** The safety and efficacy of Renagel in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery have not been established. Consequently, caution should be exercised when Renagel is used in patients with these GI disorders.

Renagel does not contain calcium or alkali supplementation; serum calcium, bicarbonate, and chloride levels should be monitored. In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, K, and folic acid levels at doses of 6–100 times the recommended human dose. In clinical trials, there was no evidence of reduction in serum levels of vitamins with the exception of a one-year clinical trial in which Renagel treatment was associated with a reduction of 25-hydroxyvitamin D (normal range 10 to 55 mcg/mL) from 39 ± 22 mcg/mL to 34 ± 22 mcg/mL (p < 0.01). Most (approximately 75%) patients in Renagel clinical trials received vitamin supplements, which is typical of patients on hemodialysis.

### Information for the Patient

The prescriber should inform patients to take Renagel with meals and adhere to their prescribed diets. Instructions should be given on concomitant medications that should be dosed apart from Renagel. Because the contents of Renagel expand in water, tablets should be swallowed intact and should not be crushed, chewed, broken into pieces, or taken apart prior to administration.

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**Figure 1. Cumulative percent of patients (Y-axis) attaining a phosphorus change from baseline at least as great as the value on the X-axis. A shift to the left of a curve indicates a better response.**

Average daily consumption at the end of treatment was 4.9 g sevelamer hydrochloride (range of 0.0 to 12.6 g) and 5.0 g of calcium acetate (range of 0.0 to 17.8 g). During calcium acetate treatment, 22% of patients developed serum calcium ≥ 11.0 mg/dL on at least one occasion versus 5% for Renagel (p < 0.05). Thus the risk of developing hypercalcemia is less with Renagel Capsules compared to calcium acetate.

Mean LDL cholesterol and mean total cholesterol declined significantly on Renagel Capsules treatment (-24% and -15%, respectively). Neither LDL nor total cholesterol changed on calcium acetate treatment. Triglycerides, high-density lipoprotein (HDL) cholesterol, and albumin did not change on either treatment.

Similar reductions in serum phosphorus and LDL cholesterol were observed in an eight-week open-label, uncontrolled study of 172 end stage renal disease patients on hemodialysis.

### Parallel study of Renagel and calcium acetate or calcium carbonate:

Two hundred ESRD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 5.5 mg/dL) following a two-week phosphate binder washout period were randomized to receive Renagel 800 mg tablets (N=99) or calcium, either calcium acetate (N=54) or calcium carbonate (N=47). Calcium acetate and calcium carbonate produced comparable decreases in serum phosphorus. At week 52, using last-observation-carried-forward, Renagel and Calcium both significantly decreased mean serum phosphorus (Table 2).

**Table 2. Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and End of Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Renagel (N=94)</th>
<th>Calcium (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus Baseline</td>
<td>7.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-2.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Ca × Phosphorus Ion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Baseline</td>
<td>70.5</td>
<td>68.4</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-19.4</td>
<td>-14.2</td>
</tr>
</tbody>
</table>

Sixty-one percent of Renagel patients and 73% of the calcium patients completed the full 52 weeks of treatment. The major reason for dropout in the Renagel group was gastrointestinal adverse events.

Figure 2, a plot of the phosphorus change from baseline for the completers, illustrates the durability of response for patients who are able to remain on treatment.
Renagel® Tablets
(sevelamer hydrochloride)

Drug interactions: Renagel Capsules were studied in human drug-drug interaction studies with ciprofloxacin, digoxin, warfarin, enalapril, metoprolol and iron.

Ciprofloxacin: In a study of 15 healthy subjects, a co-administered single dose of 7 Renagel Capsules (approximately 2.8 g) decreased the bioavailability of ciprofloxacin by approximately 50%.

Digoxin: In 19 healthy subjects receiving 6 Renagel capsules three times a day with meals for 2 days, Renagel did not alter the pharmacokinetics of a single dose of digoxin.

Warfarin: In 14 healthy subjects receiving 6 Renagel capsules three times a day with meals for 2 days, Renagel did not alter the pharmacokinetics of a single dose of warfarin.

Enalapril: In 28 healthy subjects a single dose of 6 Renagel capsules did not alter the pharmacokinetics of a single dose of enalapril.

Metoprolol: In 31 healthy subjects a single dose of 6 Renagel capsules did not alter the pharmacokinetics of a single dose of metoprolol.

Iron: In 23 healthy subjects, a single dose of 7 Renagel capsules did not alter the absorption of a single oral dose of iron as 200 mg excised ferrous sulfate tablet.

Furthermore, when administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, the drug should be administered at least one hour before or three hours after Renagel, or the physician should consider monitoring blood levels of the drug. Patients taking antiarrhythmic and anti-seizure medications were excluded from the clinical trials. Special precautions should be taken when prescribing Renagel to patients also taking these medications.

Carcinogenesis, mutagenesis, and impairment of fertility: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given sevelamer hydrochloride by diet at 0.3, 1, 3 g/kg/day. There was an increased incidence of urinary bladder transitional cell papilloma in male rats (3 g/kg/day) at exposures 2 times the maximum human oral dose of 13 g, based on a comparison of relative body surface area. Mice received mean dietary doses of 0.8, 3, 9 g/kg/day. Increased incidence of tumors was not observed in mice at exposures up to 3 times the maximum human oral dose of 13 g, based on a comparison of relative body surface area.

In an in vitro mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

In a study designed to assess potential impairment of fertility, female rats were given dietary doses of 0.5, 1.5, 4.5 g/kg/day beginning 14 days prior to mating and continuing through gestation. Male rats were given the same doses and treated for 28 days before mating. Sevelamer hydrochloride did not impair fertility in male or female rats at exposures 3 times the maximum human oral dose of 13 g, based on a comparison of relative body surface area.

Pregnancy:

Pregnancy Category C
In pregnant rats given dietary doses of 0.5, 1.5, 4.5 g/kg/day during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D occurred in the mid and high dose groups (exposures less than the maximum human dose of 13 g, based on a comparison of relative body surface area). In pregnant rabbits given oral doses of 100, 500, 1000 mg/kg/day by gavage during organogenesis an increased incidence of early resorptions occurred at exposures 2 times the maximum human dose of 13 g, based on a comparison of relative body surface area. Requirements for vitamins and other nutrients are increased in pregnancy. The effect of Renagel on the absorption of vitamins and other nutrients has not been studied in pregnant women.

Geriatric use: There is no evidence for special considerations when Renagel is administered to elderly patients.

Pediatric use: The safety and efficacy of Renagel has not been established in pediatric patients.

Renagel® Tablets
(sevelamer hydrochloride)

ADVERSE REACTIONS
In a placebo-controlled study with a treatment duration of two weeks, the adverse events reported for Renagel Capsules (N=24) were similar to those reported for placebo (N=12). In a cross-over study with treatment durations of eight weeks each, the adverse events reported for Renagel Capsules (N=82) were similar to those reported for calcium acetate (N=82) and included headache, infection, pain, hypertension, hypotension, thrombosis, diarrhea, dyspepsia, vomiting, and cough increased. In a parallel design study with treatment duration of 52 weeks, adverse events reported for Renagel Tablets (N=99) were similar to those reported for calcium (calcium acetate and calcium carbonate) (N=101). (Table 3).

Table 3. Treatment-Emergent Adverse Events ≥ 10 % from a Parallel Design Trial of Renagel Tablets versus Calcium for 52 Weeks of Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Renagel (N=99)</th>
<th>Calcium (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22.2</td>
<td>21.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>20.2</td>
<td>19.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19.2</td>
<td>22.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.1</td>
<td>11.9</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>11.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>5.1</td>
<td>10.9</td>
</tr>
<tr>
<td>Musculoskeletal, Connective Tissue and Bone Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in Limb</td>
<td>13.1</td>
<td>14.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12.1</td>
<td>17.8</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4.0</td>
<td>17.8</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>13.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10.1</td>
<td>16.8</td>
</tr>
<tr>
<td>Cough</td>
<td>7.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9.1</td>
<td>15.8</td>
</tr>
<tr>
<td>General Disorders and Site Administration Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Complication of Implant</td>
<td>6.1</td>
<td>10.9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5.1</td>
<td>10.9</td>
</tr>
</tbody>
</table>

In the parallel design study, the major reason for drop out in the Renagel group was gastrointestinal adverse events. In a long-term, open-label extension trial, adverse events possibly related to Renagel Capsules and
which were not dose-related, included nausea (7%), constipation (2%), diarrhea (4%), flatulence (4%), and dyspepsia (5%). During postmarketing experience, the following adverse events have been reported in patients receiving Renagel although no direct relationship to Renagel could be established: pruritis, rash, abdominal pain and in very rare cases, intestinal obstruction and ileus.

OVERDOSAGE
Renagel has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse effects. Renagel has been given in average doses up to 13 grams per day to hemodialysis patients. There are no reported overdosages of Renagel in patients.

Since Renagel is not absorbed, the risk of systemic toxicity is low.

DOSAGE AND ADMINISTRATION

Patients Not Taking a Phosphate Binder. The recommended starting dose of Renagel is 800 to 1600 mg, which can be administered as one to two Renagel® 800 mg Tablets or two to four Renagel® 400 mg Tablets with each meal based on serum phosphorus level. Table 4 provides recommended starting doses of Renagel for patients not taking a phosphate binder.

Table 4. Starting Dose for Patients Not Taking a Phosphate Binder

<table>
<thead>
<tr>
<th>SERUM PHOSPHORUS</th>
<th>RENAGEL® 800 MG</th>
<th>RENAGEL® 400 MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5.5 and &lt; 7.5 mg/dL</td>
<td>1 tablet three times daily with meals</td>
<td>2 tablets three times daily with meals</td>
</tr>
<tr>
<td>≥ 7.5 and &lt; 9.0 mg/dL</td>
<td>2 tablets three times daily with meals</td>
<td>3 tablets three times daily with meals</td>
</tr>
<tr>
<td>≥ 9.0 mg/dL</td>
<td>2 tablets three times daily with meals</td>
<td>4 tablets three times daily with meals</td>
</tr>
</tbody>
</table>

Patients Switching From Calcium Acetate. In a study in 84 ESRD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (mg for mg) of Renagel Capsules and calcium acetate. Table 5 gives recommended starting doses of Renagel based on a patient’s current calcium acetate dose.

Table 5. Starting Dose for Patients Switching From Calcium Acetate to Renagel

<table>
<thead>
<tr>
<th>CALCIUM ACETATE 667 MG (TABLETS PER MEAL)</th>
<th>RENAGEL® 800 MG (TABLETS PER MEAL)</th>
<th>RENAGEL® 400 MG (TABLETS PER MEAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tablet</td>
<td>1 tablet</td>
<td>2 tablets</td>
</tr>
<tr>
<td>2 tablets</td>
<td>2 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>3 tablets</td>
<td>3 tablets</td>
<td>5 tablets</td>
</tr>
</tbody>
</table>

Dose Titration for All Patients Taking Renagel. Dosage should be adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus to 5.5 mg/dL or less. The dose may be increased or decreased by one tablet per meal at two week intervals as necessary. Table 6 gives a dose titration guideline. The average dose in a Phase 3 trial designed to lower serum phosphorus to 5.0 mg/dL or less was approximately three Renagel 800 mg tablets per meal. The maximum average daily Renagel dose studied was 13 grams.

Table 6. Dose Titration Guideline

<table>
<thead>
<tr>
<th>SERUM PHOSPHORUS</th>
<th>RENAGEL DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5.5 mg/dL</td>
<td>Increase 1 tablet per meal at 2 week intervals</td>
</tr>
<tr>
<td>3.5–5.5 mg/dL</td>
<td>Maintain current dose</td>
</tr>
<tr>
<td>&lt; 3.5 mg/dL</td>
<td>Decrease 1 tablet per meal</td>
</tr>
</tbody>
</table>

Drug interaction studies have demonstrated that Renagel Capsules have no effect on the bioavailability of digoxin, warfarin, enalapril, metoprolol, or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with Renagel or calcium acetate, in a single dose study. When administering an oral drug for which alteration in blood levels could have a clinically significant effect on its safety or efficacy, the drug should be administered at least one hour before or three hours after Renagel, or the physician should consider monitoring blood levels of the drug. (See PRECAUTIONS: Drug interactions.)

Do not use Renagel after the expiration date on the bottle.

HOW SUPPLIED
Renagel® 800 mg Tablets are supplied as oval, film-coated, compressed tablets, imprinted with “RENAGEL 800,” containing 800 mg of sevelamer hydrochloride on an anhydrous basis, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. Renagel® 800 mg Tablets are packaged in bottles of 180 tablets.

NDC 58468-0021-1 Bottle of 180 Tablets

Renagel® 400 mg Tablets are supplied as oval, film-coated, compressed tablets, imprinted with “RENAGEL 400,” containing 400 mg of sevelamer hydrochloride on an anhydrous basis, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. Renagel® 400 mg Tablets are packaged in bottles of 360 tablets.

NDC 58468-0020-1 Bottle of 360 Tablets

Storage

Rx only

Distributed by:

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA
Tel. (800) 847-0069

4777
043007R03
Issued 04/07