Introduction

Phosphate is an element in the body. Formed from the mineral phosphorous, phosphate is needed to form bones and teeth, help the nerves work, and allow muscles to contract. If a person eats a diet that is too high in phosphorus, the body is usually able to efficiently eliminate the excess amount. For people with severe kidney problems or on dialysis, however, the body can’t easily eliminate excess phosphate. Phosphate binders are drugs that prevent the body from absorbing phosphorus from food. These drugs can help people with serious kidney problems maintain healthy levels of phosphate. This policy described when phosphate binding drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phoslyra® (calcium)</td>
<td>Phoslyra® (calcium acetate), Fosrenol® (lanthanum)</td>
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</table>
### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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</table>
| acetate), Fosrenol® (lanthanum carbonate), Renagel® (sevelamer HCl), Renvela® (sevelamer carbonate), Velphoro® (sucroferric oxyhydroxide) | **Auryxia® (ferric citrate) may be considered medically necessary for the treatment of hyperphosphatemia when the following criteria are met:**  
- Patient has tried and failed or had an intolerance to sevelamer HCl or sevelamer carbonate.  

**Auryxia® (ferric citrate) may be considered medically necessary for the treatment of iron deficiency anemia when the following criteria are met:**  
- Patient has tried and failed or had an intolerance to both oral iron and IV iron.  

**Note:** Examples of oral iron include ferrous fumarate, ferrous gluconate and ferrous sulfate. Examples of IV iron include ferric carboxymaltose (Injectafer®), ferric pyrophosphate citrate (Triferic®), ferumoxytol (Feraheme®), iron dextran (INFeD®), iron sucrose (Venofer®), sodium ferric gluconate complex (Ferrlecit®). |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auryxia® (ferric citrate), Phoslyra® (calcium acetate), Fosrenol® (lanthanum carbonate), Renagel® (sevelamer HCl), Renvela® (sevelamer carbonate), Velphoro® (sucroferric oxyhydroxide)</td>
<td>All other uses of Auryxia® (ferric citrate), Phoslyra® (calcium acetate), Fosrenol® (lanthanum carbonate), Renagel® (sevelamer HCl), Renvela® (sevelamer carbonate) and Velphoro® (sucroferric oxyhydroxide) for conditions not outlined in this policy are considered investigational.</td>
</tr>
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### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Auryxia® (ferric citrate), Phoslyra® (calcium acetate), Fosrenol® (lanthanum carbonate), Renagel® (sevelamer HCl), Renvela® (sevelamer carbonate) and Velphoro® (sucroferric oxyhydroxide) may be approved up to 12 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Auryxia® (ferric citrate), Phoslyra® (calcium acetate), Fosrenol® (lanthanum carbonate), Renagel® (sevelamer HCl), Renvela® (sevelamer carbonate) and Velphoro® (sucroferric oxyhydroxide) may be approved up to 1 year in duration when there is documentation of continued clinical response and that ongoing treatment is required.</td>
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</table>

### Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis and medication history

### Coding

N/A

### Related Information

### Benefit Application

The drugs in this policy are oral medications and managed through the Pharmacy benefit.
Background

Hyperphosphatemia is associated with atherosclerosis, vascular calcification, cardiovascular (CV) events, and increased mortality based on retrospective, cohort, and observational studies. Hyperphosphatemia occurs commonly with chronic kidney disease (CKD), increasing in frequency and severity as CKD worsens. Hyperphosphatemia occurs in 37% of patients on dialysis. The attributable risk of disorders of mineral metabolism in patients in dialysis is 17.5%, driven by increased risks associated with hyperphosphatemia.

Because of the relationship between hyperphosphatemia and mortality, hyperphosphatemia is commonly treated in patients with CKD. However, randomized controlled trial data linking serum phosphate to patient outcomes in is lacking in patients with CKD; therefore, treatment of hyperphosphatemia is based on epidemiologic evidence and biological plausibility.

Summary of Evidence

Meaningful Differences in Efficacy in Clinical Trials

All phosphate binders decrease phosphate significantly more than placebo and are approved on this basis for the treatment of hyperphosphatemia in patients with ESRD. A total of four large good-moderate quality meta-analyses and network meta-analysis evaluating the efficacy of phosphate binders have been completed in the last 3 years. Results were inconsistent between the meta-analyses. A single meta-analyses found iron-based binders decreased serum phosphorus more than all other binders (sevelamer, lanthanum, calcium-based binders) (OR 0.09, 95% CI 0.03-0.25). In contrast, another meta-analysis found lanthanum less effective than calcium-based binders (mean difference 0.18, 95% CI 0.10-0.25) but found no difference between sevelamer and all other binders (calcium-based, lanthanum, and iron-based). No other meta-analyses addressed this issue.

The goal of treatment with phosphate binders is to reduce mortality, cardiovascular (CV) outcomes, and bone fractures in patients with hyperphosphatemia. Long-term, placebo-controlled RCT data designed to evaluate these endpoints are lacking. The four meta-analyses mentioned above evaluated the effect of phosphate binders on all-cause mortality as well as CV mortality. Three of four meta-analyses found significantly improved all-cause mortality with sevelamer compared to calcium-based binders (RR 0.53, CI 0.30-0.91 for CKD G5D; OR 0.39, 95% CI 0.21-0.74; RR 1.89, 95% CI 1.02-3.50). The absolute mortality increase with calcium-based
binders ranged from 43-96 per 1,000 patients. The fourth meta-analysis found the same significant difference when only higher quality studies were included (RR 0.51, 95% CI 0.21-0.83; NNT 16). The meta-analysis also found sevelamer decreased mortality in comparison with calcium carbonate (RR 0.44, 95% CI 0.25-0.76) but not in comparison with calcium acetate (RR 0.43, 95% CI 0.13-1.38). Because there is a lack of placebo-controlled study data evaluating mortality, it is not known if the difference in mortality between sevelamer and calcium-based binders represents an increase in mortality with calcium-based binders, a decrease in mortality with sevelamer, or both. Based the above data, the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD-mineral and bone disorder (MBD) concluded there is a potential for benefit or an absence of harm with non-calcium-based phosphate binders compared to calcium-based agents and suggested restricting the dose of calcium-based phosphate binders.

Data was insufficient to assess changes in CV mortality in two meta-analyses. Additionally, two meta-analysis found no difference in CV mortality between groups assessed (calcium vs non-calcium-based binders RR 2.54, 95% CI 0.67-9.62; sevelamer vs calcium-based binders (RR 0.29, 95% CI 0.05-1.82). A total of two meta-analyses assessed hospitalizations; results were not consistent between meta-analyses. Sevelamer significantly decreased hospitalizations compared to calcium-based binders (RR 0.50, 95% CI 0.31-0.81, NNT 4) while no difference between lanthanum and calcium-based binders (RR 0.80, 95% CI, 0.34-1.93). Another meta-analysis found no difference in hospitalizations between calcium- and non-calcium-based binders (RR 1.28, 95% CI 0.94-1.74. The meta-analyses either did not evaluate bone fracture data or found insufficient data for evaluation.

Differences in Safety Profiles

Adverse events vary between different classes of phosphate binders.

- As discussed above, calcium-based binders are associated with increased risks of hypercalcemia (16.3%) including vascular calcification.

- Sevelamer is associated with more constipation than any other class of phosphate binders. Common AEs (≥10%) include vomiting (22%), nausea (20%), diarrhea (19%), and dyspepsia (16%). Sevelamer HCl (Renagel®) is associated with metabolic acidosis; however, this risk is not present with sevelamer carbonate (Renvela®).

- Lanthanum is associated with more nausea than other phosphate binders and more GI events than calcium-based binders. Common AEs (≥10%) include nausea (11%).
• Iron-based binders as associated with an increased risk of diarrhea compared with calcium-based agents; common AEs (≥10%) include diarrhea (21%), discolored feces (19%), and nausea (11%). Monitoring for iron accumulation is recommended and fatal poisoning is possible in children.

Evidence of Real-World Comparative Effectiveness

Data from a Phase IV, 5-year, observational cohort study comparing lanthanum and other phosphate binders found no difference in all-cause mortality (adjusted HR 0.94, 95% CI 0.88-1.01) or bone fractures requiring hospitalization (adjusted HR 0.86, 95% CI 0.71-1.05) as well as no increased risk of GI disease, liver disease, malignancy, or major infection with lanthanum.

Practice Guidelines and Position Statements

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for mineral and bone disorder were last updated in 2017 (see Table 1). The guidelines do not support the idea that all phosphate binders are interchangeable. Due to concerns about adverse events seen with calcium-based phosphate binders, the committee suggests excess exposure to calcium through diet, medications, or dialysate maybe be harmful for all patients with CKD. Of note, significant survival benefit was noted with sevelamer compared to calcium-based binders. Based on trial data, the committee concluded there is a potential for benefit or an absence of harm with calcium-free phosphate binders compared to calcium-based agents. Evidence gaps include uncertainty if effects differ between formulations of calcium-based binders and a lack of hard clinical outcomes and comparative effectiveness between binder classes. Lastly, the committee noted a lack of long-term patient centered outcomes in published Phase III trials with iron-containing phosphate binders.

Table 1. Selected KDIGO Guidelines for Lowering High Serum Phosphate and Maintaining Serum Calcium in Patients with CKD G3a-G5D

<table>
<thead>
<tr>
<th>4.1.1</th>
<th>Base treatment of CKD-MBD on serial assessments of phosphate, calcium, and PTH levels, considered together.</th>
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<tbody>
<tr>
<td>4.1.2</td>
<td>Suggest lower elevated phosphate towards the normal range.</td>
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<tr>
<td>4.1.3</td>
<td>Suggest avoiding hypercalcemia.</td>
</tr>
<tr>
<td>4.1.5</td>
<td>Base treatment decisions on phosphate-lowering on progressively or persistently elevated serum phosphate.</td>
</tr>
</tbody>
</table>
Table 1. Selected KDIGO Guidelines for Lowering High Serum Phosphate and Maintaining Serum Calcium in Patients with CKD G3a-G5D

| 4.1.6 | Suggest restricting the dose of calcium-based phosphate binders. |
| 4.1.7 | Avoid long-term use of aluminum-containing phosphate binders. |
| 4.1.8 | Suggest limiting dietary phosphate intake. |

**Notes:** G3a = GFR 45-59 ml/min/1.73m², G5D = GFR <15 ml/min/1.73m² and on dialysis

**Abbreviations:** CKD = chronic kidney disease, GFR = glomerular filtration rate, KDIGO = Kidney Disease: Improving Global Outcomes, MBD = mineral bone disease, PTH = parathyroid hormone

References

2. Phoslyra® (calcium acetate solution) prescribing information. Fresenious Medical Care North American; Waltham, MA. October 2015.
9. Velphoro® (sucroferric oxyhydroxide) chewable tablet prescribing information. Fresenius medical Care North America; Waltham, MA. April 2018.


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/01/19</td>
<td>New policy, approved April 9, 2019. Add to Prescription Drug section. Auryxia® (ferric citrate), Phoslyra, Fosrenol, Renagel, Renvela, and Velphoro may be considered medically necessary when criteria are met, considered investigational when criteria not met.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

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Chinese (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動。以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Deutsche (German):

Italiano (Italian):
Premera Blue Cross (TTY: 800-722-1471) (Korean): 

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한국어 (Korean): 

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