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Literature Scan: Phosphate Binders

Date of Review: January 2016

Date of Last Review: May 2014
Literature Search: April 2014 to December 2015

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- New evidence for phosphate binders is limited to one new systematic review for use in children with chronic kidney disease (CKD) and one new guideline for use in adults with CKD. Both publications found insufficient evidence of differences between phosphate binders in clinically relevant outcomes (bone fractures, bone deformities, bone pain, and reduced growth rates) or phosphate and PTH levels in children or adults. There is low strength evidence calcium-based phosphate binders may result in higher serum calcium levels in some patients compared to non-calcium-based phosphate binders.
- One new drug approval was identified. Auryxia™ (ferric citrate) was approved in September 2014 to control serum phosphorous levels in patients with CKD on dialysis. It is reviewed separately as a new drug evaluation.
- One new formulation was also identified. Fosrenol® (lanthanum carbonate oral powder) was approved in September 2014 based on pharmacokinetic studies that compared the powder formulation to the chewable tablet formulation already on the market.

Recommendations:
- Continue to prefer at least one calcium-based phosphate binder and one non-calcium-based phosphate binder on the Preferred Drug List (PDL).
- No changes to the current Prior Authorization (PA) are recommended (see **Appendix 4**).
- After evaluation of comparative costs in the executive session, no changes to the PDL were made.

Previous Conclusions and Recommendations:
- Phosphate binders should be selected based on each patient's specific clinical needs.
- Consider adding a non-calcium-based phosphate binder to the preferred class, based on cost. There is no evidence that shows that one agent is more effective or safer than an alternative, however there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide.
- Evaluate comparative costs in executive session.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality

(AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane Review of Interventions for Metabolic Bone Disease in Children with Chronic Kidney Disease

Cochrane reviewers updated a 2010 systematic review on interventions for metabolic bone disease in children with CKD.[1] Adverse outcomes such as bone fractures, bone deformities, bone pain, and reduced growth rates can occur in children with CKD.[1] Randomized controlled trials that compared different interventions to prevent or treat bone disease in children with CKD were eligible for inclusion in this review.[1] The review included 18 trials (n=576 children) but only 5 studies evaluated phosphate binders.[1] In 2 studies (n=29), calcium carbonate and aluminum hydroxide were used as phosphate binders and compared as interventions in pre-dialysis children with CKD.[1] There was no significant difference between the 2 interventions when mean final height, rates of hypercalcemia, or differences in serum parathyroid hormone (PTH) and phosphorous levels were assessed.[1] In 3 studies, sevelamer was compared with calcium-containing phosphate binders (calcium acetate or calcium carbonate) in patients with Stages 2 to 4 CKD.[1] There were no significant differences in the final calcium (mean difference (MD) -0.40 mg/dL, 95% CI -1.16 to 0.36; I^2=59%), phosphorus (MD 0.17 mg/dL, 95% CI 0.37 to 0.71; I^2=0%) or PTH levels (MD 51.92 pg/mL, 95% CI -77.53 to 181.36; I^2=34%) between phosphate binders.[1] However, incidence of hypercalcemia was higher with calcium-containing binders.[1] Bone histology reports also did not differ between the groups.[1] According to the reviewers, there is insufficient evidence on the effect of phosphate binders on clinically relevant outcomes (bone fractures, bone deformities, bone pain, and reduced growth rates) in children with CKD.[1]

New Guidelines:

VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) Evidence-based Practice Working Group updated their 2008 guideline for the management of CKD in 2015.[2] In CKD, hyperphosphatemia can occur in patients with CKD (eg, when glomerular filtration rate (GFR) is reduced to less than 30-35 mL/min/1.73m^2).[2] The initial approach to manage hyperphosphatemia is dietary restriction of phosphorus-containing foods.[2] However, phosphate binders are approved by the U.S. Food and Drug Administration (FDA) to control serum phosphate levels in patients with CKD.[2] Oral phosphate binders are categorized as calcium-based (eg, calcium acetate) or non-calcium-based (e.g., sevelamer, lanthanum salts, iron-based binders).[2]

Use of these phosphate binders in patients with CKD has been evaluated in placebo-controlled and comparator clinical studies.[2] Outcomes consistently studied included changes in serum calcium, phosphate and PTH levels.[2] Some studies reported calcitriol levels and few studies reported bone mineral density or vascular calcification.[2] The Guideline Working Group found the evidence for phosphate binders in patients with CKD to have conflicting and inconsistent results.[2] There were conflicting results in regard to change in serum PTH or serum phosphate levels with use of lanthanum carbonate in patients with normal baseline serum phosphorous (mean <3.5 mg/dL).[2] Use of sevelamer did not result in significant changes in serum phosphorous, PTH, calcitriol or calcidiol or bone mineral

density after 40 weeks in patients with CKD with normal baseline phosphorous levels.[2] In patients with CKD and hyperphosphatemia, however, use of calcium acetate resulted in a 50% reduction in serum PTH levels and a significant decline in serum phosphate levels, but at the expense of significant incidence of hypercalcemia.[2] In a study that randomized patients with CKD 1:1:1 using calcium acetate, sevelamer and lanthanum versus placebo, there were not significant changes found in serum PTH levels with active therapy but there was a 21% increase in PTH levels of patients who received placebo.[2] Serum phosphate was significantly lower in patients who received lanthanum.[2] The calcium acetate group showed significant improvement in annualized bone density.[2] Patients on an active phosphate binder were more likely to have progression of coronary calcification compared to patients on placebo (38% vs. 17%; p=0.03).[2] Another study confirmed the beneficial effects of calcium acetate and sevelamer on serum phosphorus levels in CKD patients with hyperphosphatemia but both groups had a significant increase in serum PTH levels after only 8 weeks.[2]

The guideline does not recommend use of phosphate binders in patients with normal serum phosphorous levels based on insufficient evidence and possible increased risk of vascular calcification (weak recommendation against use).[2] However, oral phosphate binders may be considered in patients with CKD and hyperphosphatemia that do not respond to dietary interventions alone.[2]

New FDA Drug Approvals:
Auryxia® (ferric citrate) was approved September 2014 as a phosphate binder to control serum phosphorous levels in patients with CKD on dialysis.[3] The drug is evaluated separately in a new drug evaluation.

New Formulations/Indications:
Fosrenol® (lanthanum carbonate) oral powder for oral use was approved by the FDA in September 2014 based on pharmacokinetic studies.[4] The new formulation of lanthanum carbonate joins the chewable tablet formulation already marketed. Both formulations are indicated as phosphate binders to reduce serum phosphate in patients with CKD.[4]

New FDA Safety Alerts:
None identified.

References:

1. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. *Cochrane Database of Systematic Reviews*. 2015; Issue 11. Art. No.: CD008327. DOI: 10.1002/14651858.CD008327.pub2.
2. The Management of Chronic Kidney Disease Working Group, Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care. Version 3.0; 2014. Available at http://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG.pdf. Accessed December 3, 2015.
3. Auryxia (ferric citrate) tablets [Prescribing Information]. New York, NY: Keryx Biopharmaceuticals, Inc., July 2015.
4. Fosrenol (lanthanum carbonate) oral powder [Prescribing Information]. Wayne, PA: Shire US Inc., September 2014.

Author: Andrew Gibler, Pharm.D. Date: March 2016

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	CALCIUM ACETATE	CALCIUM ACETATE	Y
ORAL	CAPSULE	PHOSLO	CALCIUM ACETATE	Y
ORAL	TABLET	CALCIUM ACETATE	CALCIUM ACETATE	Y
ORAL	TABLET	CALPHRON	CALCIUM ACETATE	Y
ORAL	TABLET	ELIPHOS	CALCIUM ACETATE	Y
ORAL	TABLET	RENAGEL	SEVELAMER HCL	Y
ORAL	POWD PACK	FOSRENOL	LANTHANUM CARBONATE	N
ORAL	POWD PACK	RENVELA	SEVELAMER CARBONATE	N
ORAL	SOLUTION	PHOSLYRA	CALCIUM ACETATE	N
ORAL	TAB CHEW	FOSRENOL	LANTHANUM CARBONATE	N
ORAL	TAB CHEW	VELPHORO	SUCROFERRIC OXYHYDROXIDE	N
ORAL	TABLET	AURYXIA	FERRIC CITRATE	N
ORAL	TABLET	MAGNEBIND 300	CALCIUM CARBONATE/MAG CARB	N
ORAL	TABLET	MAGNEBIND 400 RX	CALCIUM CARBONATE/MAG CARB/FA	N
ORAL	TABLET	RENVELA	SEVELAMER CARBONATE	N

Appendix 2: New Clinical Trials

A total of 44 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2015

1 calcium acetate.mp. 293

2 sevelamer.mp. 698

3 lanthanum carbonate.mp. 348

4 sucroferric oxyhydroxide.mp. 6

5 ferric citrate.mp. 653

6 1 or 2 or 3 or 4 or 5 1762

7 limit 6 to (english language and yr="2014 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 44

Phosphate Binders

Goal(s):

- Promote use of preferred drugs.
- Reserve non-calcium-based phosphate binders for second-line therapy.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred phosphate binders
- Preferred non-calcium-based phosphate binders

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Go to #5
3. Has the patient tried or contraindicated to calcium acetate?	**Yes:** Document trial dates and/or intolerance and go to #4.	**No:** Pass to RPh. Deny for medical appropriateness. Recommend trial of preferred calcium acetate product.
4. Will the prescriber consider a change to a preferred non-calcium-based phosphate binder?	**Yes:** Approve for 1 year and inform prescriber of preferred alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.
5. RPh only: All other indications need to be evaluated as to whether use is for an OHP-funded diagnosis. • If funded and clinic provides supporting literature, approve for up to 12 months. • If non-funded, deny (not funded by the OHP).		

P&T/DUR Review: *1/16 (AG); 11/12; 9/12; 9/10*
Implementation: *2/21/13*