VELPHORO® (sucroferric oxyhydroxide) chewable tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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Description:

Velphoro (sucroferric oxyhydroxide) is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis.

Changes in bone mineral metabolism and deviations in calcium and phosphate balance occur early in CKD. These changes progress as kidney function declines. They are grouped under the term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) which includes renal osteodystrophy and extraskeletal (vascular) calcification related to these abnormalities. Renal osteodystrophy includes osteitis fibrosa (hyperparathyroidism), osteomalacia, and adynamic bone disease.

Patients with CKD-MBD are at higher risk of death. CKD leads to hyperphosphatemia and a number of chronic disturbances of calcium-phosphate homeostasis. As kidney function declines, the ability to regulate and eliminate phosphorus declines. There are several complications from hyperphosphatemia: conversion of 24-hydroxyvitamin D to 1, 25-dihydroxyvitamin D (calcitriol) is inhibited, there is a decrease in the intestinal absorption of calcium...
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leading to hypocalcemia, and development of renal bone loss, extraosseous calcification of soft tissue and
vasculature, and an increased risk of death. The risk for death is increased with hyperphosphatemia > 6.5 mg/dL.
Low levels of calcitriol and low levels of calcium with hyperphosphatemia also stimulate the secretion of
parathyroid hormone (PTH). Secondary hyperparathyroidism contributes to abnormal bone metabolism in CKD.

Management of the bone disorder includes maintain calcium and phosphorus balance and vitamin D
supplementation. CKD patients on dialysis should have a goal serum phosphorus level between 3.5-5.5 mg/dL
and a goal total serum calcium level (corrected for serum albumin) of 8.4-9.5 mg/dL. A calcium-phosphorus
product (Ca x P) can be calculated using the patient’s total serum calcium (corrected for serum albumin) and
serum phosphorus. Patients with an elevated Ca x P are at significantly higher risk of death. The desired Ca x P
product level is less than 55 mg²/dL².

It is recommended that patients with CKD stages 3-5 and CKD stage 5D (dialysis) use phosphate-binding agents
for the treatment of hyperphosphatemia. Studies have shown that all phosphate lowering medications (calcium
salts, aluminum salts, magnesium salts, sevelamer and lanthanum carbonate) are effective in lowering serum
phosphorus levels. It is recommended that calcium-based phosphate binders not be used in the presence of
persistent or recurrent hypercalcemia (a corrected calcium of > 10.2 mg/dL), arterial calcification, adynamic bone
disease, and two consecutive serum intact PTH levels that are persistently low (< 150 pg/mL). Furthermore, it is
recommended to avoid the long-term use of aluminum containing phosphate binders, as they may cause
neurotoxicity and impair bone mineralization.

The data remain inconclusive as to whether there is a difference in long-term clinical outcome benefit among the
phosphate binders (i.e., calcium based phosphate binders compared to non-calcium based phosphate binders).

Velphoro (sucroferric oxyhydroxide) binds phosphate in the gastrointestinal (GI) tract. The bound phosphate is
eliminated within the feces. Both serum phosphorus levels and calcium-phosphorus product levels are reduced as a
consequence of the reduced dietary phosphate absorption.

Each Velphoro (sucroferric oxyhydroxide) contains 500 mg of iron in 2,500 mg sucroferric oxyhydroxide, a
degradation product, a mononuclear iron species can be released and a minimal amount is absorbed. The
sucrose and starch components can be digested to glucose and fructose, and maltose and glucose respectively
and they can be absorbed. One tablet is equivalent to 1.4 g of carbohydrates.

Definitions:

Calculation for corrected calcium:

Corrected calcium = serum calcium + 0.8 (4 – serum albumin)

Ex. Calcium 9.9 mg/dl; albumin 3.2 gm/dl
Corrected calcium = 9.9 + 0.8 (4 - 3.2)
Corrected calcium = 10.54 (10.5 mg/dl)
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Stages of CKD:

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Normal kidney or high</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function</td>
</tr>
<tr>
<td>3 A</td>
<td>45-59</td>
<td>Mild to moderately reduced kidney function</td>
</tr>
<tr>
<td>3 B</td>
<td>30-44</td>
<td>Moderate to severely reduced kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced kidney function</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15 or on dialysis</td>
<td>End stage kidney failure (sometimes called established renal failure)</td>
</tr>
</tbody>
</table>

Suffixes:
- p: means there is significant proteinuria (Ex. Stage 3Ap)
- T: indicates the patients has a renal transplant (Ex. Stage 3AT)
- D: indicates the patient is on dialysis (Ex. Stage 5 D)

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.
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If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Velphoro (sucroferric oxyhydroxide) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Velphoro (sucroferric oxyhydroxide) is considered medically necessary when ALL of the following criteria are met:
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1. Individual is 18 years of age or older

2. Medical record documentation of a confirmed diagnosis of chronic kidney disease on dialysis with hyperphosphatemia (≥ 5.5 mg/dL) with ANY of the following:
   - Evidence of bone disease
   - Individual with vascular and/or other soft tissue calcification
   - Elevated corrected serum calcium of ≥ 10.2 mg/dL OR two consecutive low iPTH levels of < 150 pg/mL, with a normal or elevated corrected serum calcium

3. ALL of the following baseline tests have been completed before initiation of treatment:
   - Serum phosphorus
   - Serum calcium
   - Serum albumin
   - Intact parathyroid hormone level

4. Medical record documentation that the individual is unable to use ALL of the following due to a failed response, significant adverse drug event or contraindication:
   - Eliphos (calcium acetate)
   - Fosrenol (lanthanum)
   - Renagel (sevelamer HCl)
   - Renvela (sevelamer carbonate) or generic sevelamer carbonate

5. Absence of ALL of the following exclusions:
   - Velphoro should not be prescribed with oral levothyroxine

   Velphoro (sucroferric oxyhydroxide) for all other indications not previously listed is considered experimental or investigational based upon:

   1. Lack of final approval from the Food and Drug Administration, and
   2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
   3. Insufficient evidence to support improvement of the net health outcome, and
   4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
   5. Insufficient evidence to support improvement outside the investigational setting.

Resources:


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Velphoro is a phosphate binder indicated for the control of serum phosphorus</td>
<td>Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, tablets may be crushed.</td>
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<tr>
<td>levels in patients with chronic kidney disease on dialysis.</td>
<td>The recommended starting dose of Velphoro is 3 tablets (1,500 mg) per day, administered as 1 tablet (500 mg) 3 times daily with meals.</td>
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<td></td>
<td>Adjust by 1 tablet per day as needed until an acceptable serum phosphorus level is reached, with regular monitoring afterwards. Titrate as often as weekly.</td>
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