Velphoro (sucroferric oxyhydroxide)

STRENGTH	DOSAGE FORM	ROUTE	GPID
500mg	chewable tablet	oral	36003

MANUFACTURER

Fresenius Medical Care North America

INDICATION(S)

For the control of serum phosphorus levels in patients with chronic kidney disease on dialysis

DRUG CLASS

ELECTROLYTE REGULATION; ELECTROLYTE DEPLETERS

PLACE IN THERAPY

Velphoro is the first iron-based, calcium-free phosphate binder. Other calcium- and aluminum-free phosphate binders include sevelamer HCl, sevelamer carbonate, and lanthanum carbonate. Calcium-based phosphate binders (e.g., calcium acetate and calcium carbonate) and magnesium-based phosphate binders (e.g., Magnebind) are also available. Sevelamer carbonate is often recognized as the current standard of care for patients with chronic kidney disease on dialysis but is associated with high pill burden. Calcium acetate has long been recognized as an effective phosphate binder and is available as a generic gelcap/capsule. However, calcium levels must be closely monitored in patients taking calcium-based phosphate binders, and concern exists regarding arterial calcification as well as possible increased cardiovascular mortality with long-term use of these agents. Aluminum-based phosphate binders are rarely used due to the concern for tissue accumulation and toxicity.

Specific guidelines for hyperphosphatemia (e.g., target serum phosphorous levels, dietary restrictions and use of phosphate binders) are available from National Institute for Health and Clinical Excellence (NICE), Kidney Disease: Improving Global Outcomes (KDIGO), and National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Due to the lack of quality evidence many of these recommendations are based on opinion. The guidelines provide specific target goals for phosphorus and recommend tailoring therapy based on individual patient characteristics. The NICE guidelines recommend that calcium containing phosphate binders are used as first line agents and outline an algorithm that directs the prescriber when to consider other therapies and/or combination therapy. For chronic kidney disease (CKD) patients with kidney failure (Stage 5), both calcium-based phosphate binders and other non-calcium, non-aluminum, non-magnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels. Either agent may be used as the primary therapy and in dialysis patients who remain hyperphosphatemic (serum phosphorus >5.5 mg/dL [1.78 mmol/L]) despite the use of either of calcium-based phosphate binders or other non-calcium, non-aluminum, non-magnesium-containing phosphate-binding agents, a combination of both is often used. The KDIGO guideline recommends individualized therapy and provides parameters for restricting use of calcium containing phosphate binders in certain populations (i.e. those with hypercalcemia, arterial calcifications, etc). NKF KDOQI guidelines recommend calcium containing binders as first line in CKD patients but note that any of the binders are appropriate for ESRD patients as primary

therapy, however, aluminum-containing phosphate binders should generally be reserved for serum phosphorus levels >7.0 and for short-term use only. Combination therapy is also mentioned in the KDOQI guidelines but is based on opinion and not on evidence.
Velphoro offers another calcium-free option in the treatment of hypophosphatemia with similar efficacy and tolerability as current agents. One potential advantage of Velphoro would be reduction in pill burden.

EFFICACY

The ability of Velphoro to lower serum phosphorus in ESRD patients on dialysis was demonstrated in two randomized clinical trials: one 6-week, open-label, active-controlled (sevelamer hydrochloride), dose-finding study; and one 55-week, open-label, active-controlled (sevelamer carbonate), parallel-group, safety and efficacy study.

In clinical trials, control of serum phosphorus levels was demonstrated at doses starting from 1,000 mg (2 tablets) per day with treatment effect being observed as early as 1-2 weeks after starting Velphoro.

In a dose titration Study-05A, 1,054 patients on hemodialysis (n=968) or peritoneal dialysis (n=87) with serum phosphorus ≥6 mg/dL following a 2-4 week phosphate binder washout period, were randomized and treated with either Velphoro, at a starting dose of 1,000 mg/day (n=707), or active control (sevelamer carbonate, n=348) for 24 weeks. At the end of Week 24, 93 patients on hemodialysis whose serum phosphorus levels were controlled (<5.5 mg/dL) with Velphoro in the first part of the study, were re-randomized to continue treatment with either their Week 24 maintenance dose (n=44) or a non-effective low dose control of 250 mg/day (n=49) of Velphoro for a further 3 weeks. At Week 27, a superiority analysis of the Velphoro maintenance dose versus low dose was performed. The maximum dose of Velphoro was 3,000 mg/day (6 tablets/day) and the minimum dose was 1,000 mg/day (2 tablets/day). Velphoro was administered with food and the daily dose was divided across the largest meals of the day.

The Velphoro maintenance dose (1,000 to 3,000 mg/day) was statistically significantly superior in sustaining the phosphorus lowering effect in hemodialysis patients at Week 27 ($p<0.001$) compared with the non-effective low dose control. The results are provided in the table 1 (from Velphoro prescribing information):

Table 1 Mean (SD) Serum Phosphorus and Change from Baseline to End of Treatment

	Mean (SD) Serum Phosphorus (mg/dL)	
	Velphoro Maintenance Dose (1,000 to 3,000 mg/day) (N=44)	Velphoro Low Dose Control (250 mg/day) (N=49)
Week 24 (BL)	4.7 (1.03)	5.0 (1.14)
Week 25	4.7 (0.91)	6.3 (1.44)
Week 26	4.7 (1.21)	6.6 (1.91)
Week 27/End of Treatment	5.0 (1.07)	6.8 (1.63)
Change from BL to End of Treatment	0.3 (1.22)*	1.8 (1.47)

* $p<0.001$ for the difference in least square means of the change from BL to Week 27/End of Treatment (LOCF principle) between Velphoro maintenance dose and low dose using a covariance analysis (MIXED Model).
Notes: BL is Week 24 or latest value available before Week 24 when Week 24 result is missing; End of Treatment is Week 27 value or includes the latest evaluable measurement after Week 24 (i.e., LOCF).
BL = Baseline; LOCF = Last observation carried forward; SD = Standard deviation.

Following completion of Study-05A, 658 patients (597 on hemodialysis and 61 on peritoneal dialysis) were treated in a 28-week extension study (Study-05B) with either Velphoro (n=391) or sevelamer carbonate (n=267) according to their original randomization.

Age, gender, race, or dialysis modality did not affect the efficacy of Velphoro. Serum phosphorus levels declined rapidly during the first few weeks of treatment and remained relatively constant thereafter. The phosphorus lowering effect of Velphoro was consistently maintained through 12 months of treatment (shown in Figure 1), *from Velphoro prescribing information:*

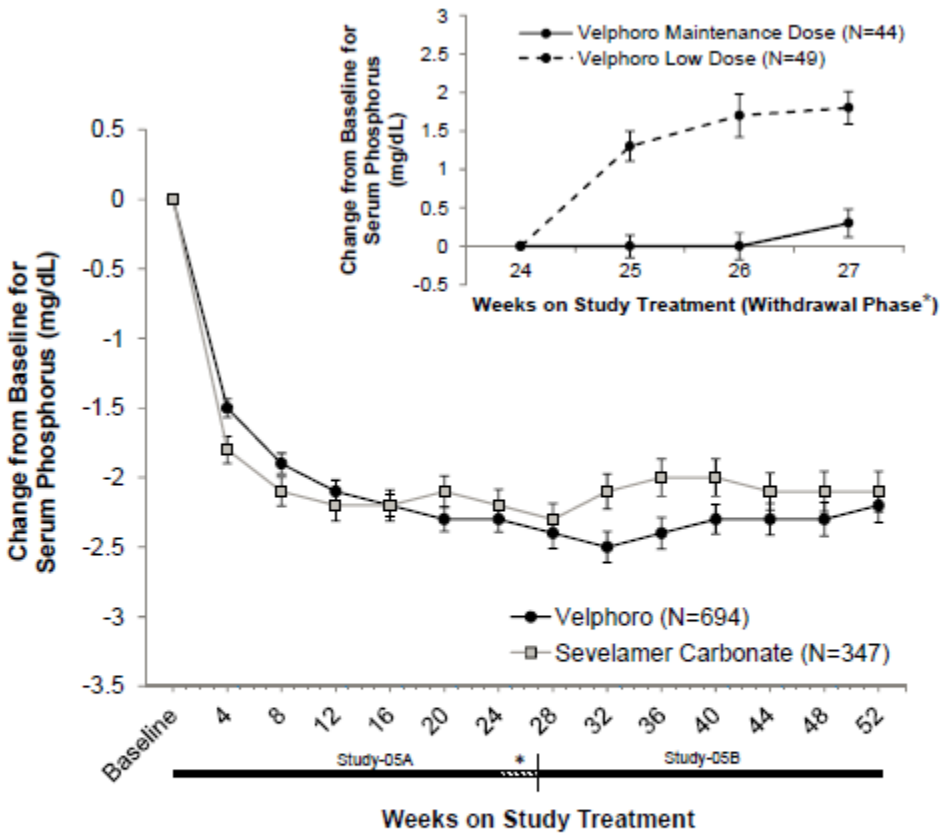

Figure 1 Mean change (±SEM) from baseline in serum phosphorus over time in Study-05A and extension Study-05B. Insert showing the mean change (±SEM) from baseline in serum phosphorus during the withdrawal phase of the study (Weeks 24 to 27) for Velphoro non-effective low dose control (250 mg/day) versus Velphoro maintenance dose.

SAFETY

The safety data derived from Velphoro clinical trials reflect exposure to Velphoro in 2 active-controlled clinical studies involving a total of 778 patients on hemodialysis and 57 patients on peritoneal dialysis exposed for up to 55 weeks. Dosage regimens ranged from 250 mg to 3,000 mg per day.

The most common adverse events observed in clinical trials were discolored (dark colored) feces and diarrhea.

The serum iron levels in patients treated with Velphoro did not differ significantly compared to active control and there was no evidence of iron accumulation during one year of treatment.

Velphoro should be administered at least one hour after alendronate and doxycycline. Velphoro should not be prescribed with oral levothyroxine and oral vitamin D analogs.

Clinical trials did not include patients with significant gastric or hepatic disorders, those who had undergone major gastrointestinal surgery, those with peritonitis during peritoneal dialysis, or those with

hemochromatosis or other iron accumulation diseases; drug effects and iron homeostasis should be monitored closely in these patients.

Velphoro is pregnancy category B.

DOSAGE

The recommended starting dose of Velphoro is three tablets (1,500 mg) per day, administered as 1 tablet (500 mg) three times daily with meals. The tablets must be chewed and not swallowed whole. The tablets may be crushed for ease of administration.

Serum phosphorus levels should be monitored and the dose of Velphoro titrated by 500 mg (1 tablet) per day as needed until an acceptable serum phosphorus level (less than or equal to 5.5 mg/dL) is reached, with regular monitoring afterwards.

COST

Drug	Cost/unit	Cost per 30 Days
Velphoro (sucroferric oxyhydroxide) 500mg chewable tab	AWP=$11.40	$1026-$2052
calcium carbonate 1250mg tablet (many formulations available)	MAC=$0.08	$8
Magnebind 400 RX 200-400-1mg tablet (magnesium carbonate/calcium carbonate/FA)	AWP=$0.26	$23-70
calcium acetate 667mg capsule	MAC=$0.56	$101-$151
Phoslyra (calcium acetate) 667mg per 5mL oral solution	AWP=$0.20/mL	$108-$270
Renvela (sevelamer carbonate) powder 0.8g and 2.4g powder packets	AWP=$10.47 (per packet; both strengths)	$942-$1885
Renvela (sevelamer carbonate) 800mg tablets	AWP=$3.49	$314-$1571
Renagel (sevelamer HCl) 800mg tablets (400mg tablets also available)	AWP=$4.36 (800mg)	$1177
Fosrenol (lanthanum carbonate) 500, 750, 1000mg chew tabs	AWP=$9.53 (all strengths)	$858

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Velphoro to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Dasgupta, I, et al. Management of Hyperphosphatemia in Chronic Kidney Disease: Summary of National Institute for Health and Clinical Excellence (NICE) Guidelines. Nephron Clin Pract. 2013; 1241: 1-9.
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- Jamal S, Vandermeer B, Raggi P, Mendelssohn D, and Chatterly T, et al. Effect of calcium-based versus non-calcium based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet 2013; 382 (9900):1268-1277.
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- National Kidney Foundation. KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD). AM J Kidney Disease 2010; 55:773-799.
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