HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VELPHORO® safely and effectively. See full prescribing information for VELPHORO®.

VELPHORO® (sucroferric oxyhydroxide) chewable tablet for oral use
Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE ----------

- Velphoro is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. (1)

---------- DOSAGE AND ADMINISTRATION----------

- Chew or crush Velphoro tablets, do not swallow whole. (2)
- 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. (2)
- 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. (2)

----------DOSAGE FORMS AND STRENGTHS ----------

- Velphoro (sucroferric oxyhydroxide) chewable tablet 500 mg (3)

---------- CONTRAINDICATIONS----------

- None.

----------WARNINGS AND PRECAUTIONS ----------

- Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients. (5.1)

----------ADVERSE REACTIONS ----------

- In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Medical Care North America at 1-800-323-5188 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS ----------

- Velphoro can be administered concomitantly with oral calcitriol, ciprofloxacin, digoxin, enalapril, furosemide, HMG‑CoA reductase inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin. (7)
- Take acetylsalicylic acid, cephalexin and doxycycline at least 1 hour before Velphoro. (7)
- Take levothyroxine at least 4 hours before Velphoro. (7)
- For oral medications not listed above where a reduction of bioavailability would be clinically significant consider separation of the timing of administration. Consider monitoring clinical responses or blood levels of the concomitant medication (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

Velphoro chewable tablets should be chewed or crushed. Do not swallow whole.

Starting Dose

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.

Titration and Maintenance

Monitor serum phosphorus levels and titrate the dose of Velphoro in decrements or increments of 500 mg (1 tablet) per day as needed until an acceptable serum phosphorus level is reached, with regular monitoring afterwards. Titrate as often as weekly.

Based on clinical studies, on average patients required 3 to 4 tablets (1,500 mg to 2,000 mg) a day to control serum phosphorus levels.

The highest daily dose studied in a Phase 3 clinical trial in ESRD patients was 6 tablets (3,000 mg) per day.

Administration

Velphoro must be administered with meals. To maximize the dietary phosphate binding, distribute the total daily dose among meals. No additional fluid above the amount usually taken by the patient is required.

If one or more doses of Velphoro are missed, the medication should be resumed with the next meal. Do not attempt to replace a missed dose.

3 DOSAGE FORMS AND STRENGTHS

Velphoro (sucroferric oxyhydroxide) chewable tablet 500 mg.

Each chewable tablet contains 500 mg iron (equivalent to 2,500 mg sucroferric oxyhydroxide).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring in Patients with Gastrointestinal Disorders or Iron Accumulation Disorders

Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal (GI) surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

In a parallel design, dose-finding study of Velphoro with a treatment duration of 6 weeks in hemodialysis patients, adverse reactions for Velphoro (N=128) were similar to those reported for the active-control group (sevelamer hydrochloride) (N=26), with the exception of discolored feces (12%) which did not occur in the active-control group. Diarrhea was reported in 6% of patients treated with Velphoro. In a 55-week, open-label, active-controlled, parallel design, safety and efficacy study involving 968 hemodialysis patients and 86 peritoneal dialysis patients treated with either Velphoro (N=707 including 57 peritoneal dialysis patients) or the active-control (sevelamer carbonate) (N=348 including 29 peritoneal dialysis patients), adverse reactions occurring in more than 5% in the Velphoro group were diarrhea (24%), discolored feces (16%), and nausea (10%). The majority of diarrhea events in the Velphoro group were mild and transient, occurring soon after initiation of treatment, and resolving with continued treatment. Adverse reactions occurred at similar rates in hemodialysis and peritoneal dialysis patients. The most common adverse reactions

(>1%) leading to withdrawal were diarrhea (4%), product taste abnormal (2%), and nausea (2%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Velphoro that are not included in other sections of labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: tooth discoloration

Skin and Subcutaneous Tissue Disorder: rash

7 DRUG INTERACTIONS

Table 1 Oral drugs that can be administered concomitantly with Velphoro

Calcitriol Ciprofloxacin Digoxin Enalapril Furosemide HMG-CoA reductase inhibitors Hydrochlorothiazide Losartan Metoprolol Nifedipine Omeprazole Quinidine Warfarin
Oral drugs that are to be separated from Velphoro and meals

	Dosing Recommendations
Doxycycline Acetylsalicylic acid Cephalexin	Take at least 1 hour before Velphoro.
Levothyroxine	Take at least 4 hours before Velphoro

Oral medications not listed in Table 1

There are no empirical data on avoiding drug interactions between Velphoro and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separating the administration of the two drugs. The necessary separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Where possible, consider monitoring for clinical response and/or blood levels of concomitant medications that have a narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 16 and 4 times, respectively, the human maximum recommended clinical dose on a body weight basis, and have not revealed evidence of impaired fertility or harm to the fetus due to Velphoro *[see Nonclinical Toxicology (13.2)]*. However, Velphoro at a dose up to 16 times the maximum clinical dose was associated with an increase in post-implantation loss in pregnant rats. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies in pregnant women.

8.2 Labor and Delivery

No Velphoro treatment-related effects on labor and delivery were seen in animal studies with doses up to 16 times the maximum recommended clinical dose on a body weight basis. The effects of Velphoro on labor and delivery in humans are not known.

8.3 Nursing Mothers

Since the absorption of iron from Velphoro is minimal *[see Clinical Pharmacology (12.3)]*, excretion of Velphoro in breast milk is unlikely.

8.4 Pediatric Use

The safety and efficacy of Velphoro have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects in two active-controlled clinical studies of Velphoro (N=835), 29.7% (n=248) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

10 OVERDOSAGE

There are no reports of overdosage with Velphoro in patients. Since the absorption of iron from Velphoro is low *[see Clinical Pharmacology (12.3)]*, the risk of systemic iron toxicity is low. Hypophosphatemia should be treated by standard clinical practice.

Velphoro has been studied in doses up to 3,000 mg per day.

11 DESCRIPTION

Velphoro chewable tablets are brown, circular, bi-planar, and are embossed with "PA 500" on 1 side. Each tablet of Velphoro contains 500 mg iron (in 2,500 mg sucroferric oxyhydroxide). The Velphoro drug substance is a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches. One tablet is equivalent to approximately 1.4 g of carbohydrates (750 mg sucrose and 700 mg starches). The active moiety, polynuclear iron(III)-oxyhydroxide, is practically insoluble and cannot be absorbed. The inactive ingredients are berry flavor, neohesperidin dihydrochalcone, magnesium stearate, and silica (colloidal, anhydrous).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In the aqueous environment of the GI tract, phosphate binding takes place by ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and the phosphate in the diet. The bound phosphate is eliminated with feces.

Both serum phosphorus levels and calcium-phosphorus product levels are reduced as a consequence of the reduced dietary phosphate absorption.

12.2 Pharmacodynamics

In vitro studies have demonstrated a robust phosphate binding capacity of Velphoro over the physiologically relevant pH range of the GI tract (1.2-7.5). The phosphate binding capacity of Velphoro peaked at pH 2.5, resulting in 96% of the available phosphate being adsorbed (phosphorus:iron concentration ratio 0.4:1).

12.3 Pharmacokinetics

The active moiety of Velphoro, polynuclear iron(III)-oxyhydroxide (pn-FeOOH), is practically insoluble and therefore not absorbed and not metabolized. Its degradation

product, mononuclear iron species, can however be released from the surface of pn-FeOOH and be absorbed.

Because of the insolubility and degradation characteristics of Velphoro, no classical pharmacokinetic studies can be carried out.

The sucrose and starch components of Velphoro can be digested to glucose and fructose, and maltose and glucose, respectively. These compounds can be absorbed in the blood.

The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day, was investigated in 16 chronic kidney disease patients (8 pre-dialysis and 8 hemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L). In healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on Day 21. In chronic kidney disease patients, the median uptake was much less, 0.04% on Day 21.

Drug Interaction Studies

In vitro

In vitro interactions were studied in aqueous solutions which mimic the physico-chemical conditions of the gastro-intestinal tract with or without the presence of phosphate (400 mg). The study was conducted at pH 3.0, 5.5 and 8.0 with incubation at 37°C for 6 hours.

Interaction with Velphoro was seen with the following drugs: alendronate, doxycycline, acetylsalicylic acid, cephalexin, levothyroxine, and paricalcitol.

The following drugs did not show interaction with Velphoro: ciprofloxacin, enalapril, hydrochlorothiazide, metoprolol, nifedipine, and quinidine.

In vivo

Five *in vivo* drug interaction studies (N=40/study) were conducted with losartan, furosemide, digoxin, omeprazole and warfarin in healthy subjects receiving 1,000 mg Velphoro 3 times a day with meals. Velphoro did not alter the systemic exposure as measured by the area under the curve (AUC) of the tested drugs when co-administered with Velphoro or given 2 hours later.

Data from the clinical studies (Study-05A and Study-05B) show that Velphoro does not affect the lipid lowering effects of HMG-CoA reductase inhibitors or the PTH lowering effect of calcitriol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were performed in mice and rats.

In the 2-year carcinogenicity study in mice, animals were given Velphoro by diet at doses of 250, 500 or 1,000 mg/kg/day. There was no clear evidence of a carcinogenic effect in mice. Mucosal hyperplasia, with diverticulum/cyst formation was observed in the colon and caecum of mice after 2 years treatment. In the 2-year rat carcinogenicity study, animals were given Velphoro by diet at doses of 40, 150 or 500 mg/kg/day. No statistically significantly increased incidences of tumors were found, but there were increased incidences in epithelial hyperplasia with or without submucosal inflammation in duodenum, cecum and colon at the dose of 500 mg/kg/day (10 times the maximum recommended clinical dose).

Velphoro was not mutagenic, clastogenic or DNA damaging *in vitro* in the Ames bacterial reverse mutation test, or in the Chinese-hamster fibroblast chromosomal aberration test, or *in vivo* in the rat Comet assay or peripheral blood micronucleus test.

In rats, mating performance and fertility were unaffected by Velphoro at oral doses up to 800 mg/kg/day (16 times the maximum recommended clinical dose).

13.2 Animal Toxicity and/or Pharmacology

In pregnant rats given up to 800 mg/kg/day Velphoro by oral gavage from Days 6 to 17 post-mating, no embryo-fetal development toxicity was observed. This dose corresponds to 16 times the maximum recommended clinical dose.

In pregnant rabbits given 50, 100 or 200 mg/kg/day Velphoro by oral gavage, from Days 6 to 19 post-mating, the number of fetuses with incomplete/unossified epiphyses and metacarpals/phalanges was increased at the highest dose (corresponding to 4 times the recommended maximum clinical dose). Litter parameters were not adversely affected.

In pregnant rats given Velphoro at 100, 280, or 800 mg/kg/day by oral gavage from Day 6 post-mating to lactation Day 20, offspring body weight gain was lower at age 5-13 weeks and neuromuscular function was delayed at the dose of 800 mg/kg/day. This dose represented 16 times the maximum recommended clinical dose.

14 CLINICAL STUDIES

The ability of Velphoro to lower serum phosphorus in ESRD patients on dialysis was demonstrated in 2 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.

14.1 Fixed-dose Study

In Study-03A, 154 ESRD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL but <7.75 mg/dL) following a 2-week phosphate binder washout period, were randomized to receive Velphoro at 250 mg/day, 1,000 mg/day, 1,500 mg/day, 2,000 mg/day, or 2,500 mg/day or active-control (sevelamer hydrochloride). Velphoro treatment was divided across meals, depending on dose. No dose titration was allowed. Within each of the groups, the serum phosphorus level at the end of treatment was compared to baseline value. Velphoro was shown to be efficacious ($p \leq 0.016$) for all doses except 250 mg/day. There were no patient-reported dose limiting treatment-emergent adverse events.

Mean changes in iron parameters (ferritin, transferrin saturation (TSAT) and transferrin) and vitamins (A, D, E and K) were generally not clinically meaningful and showed no apparent trends across the treatment groups. Velphoro had a similar GI adverse event profile *[see Adverse Reactions (6.1)]* to sevelamer hydrochloride, and no dose-dependent trend in GI events was observed.

14.2 Dose Titration Study

In Study-05A, 1,055 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 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 Table 2.

Table 2 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 the 28-week extension study (Study-05B) with either Velphoro (N=391) or sevelamer carbonate (N=267) according to their original randomization.

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 and controlled through 12 months of treatment (shown in Figure 1). The proportion of adherent patients for Velphoro was 86% at 52 weeks.

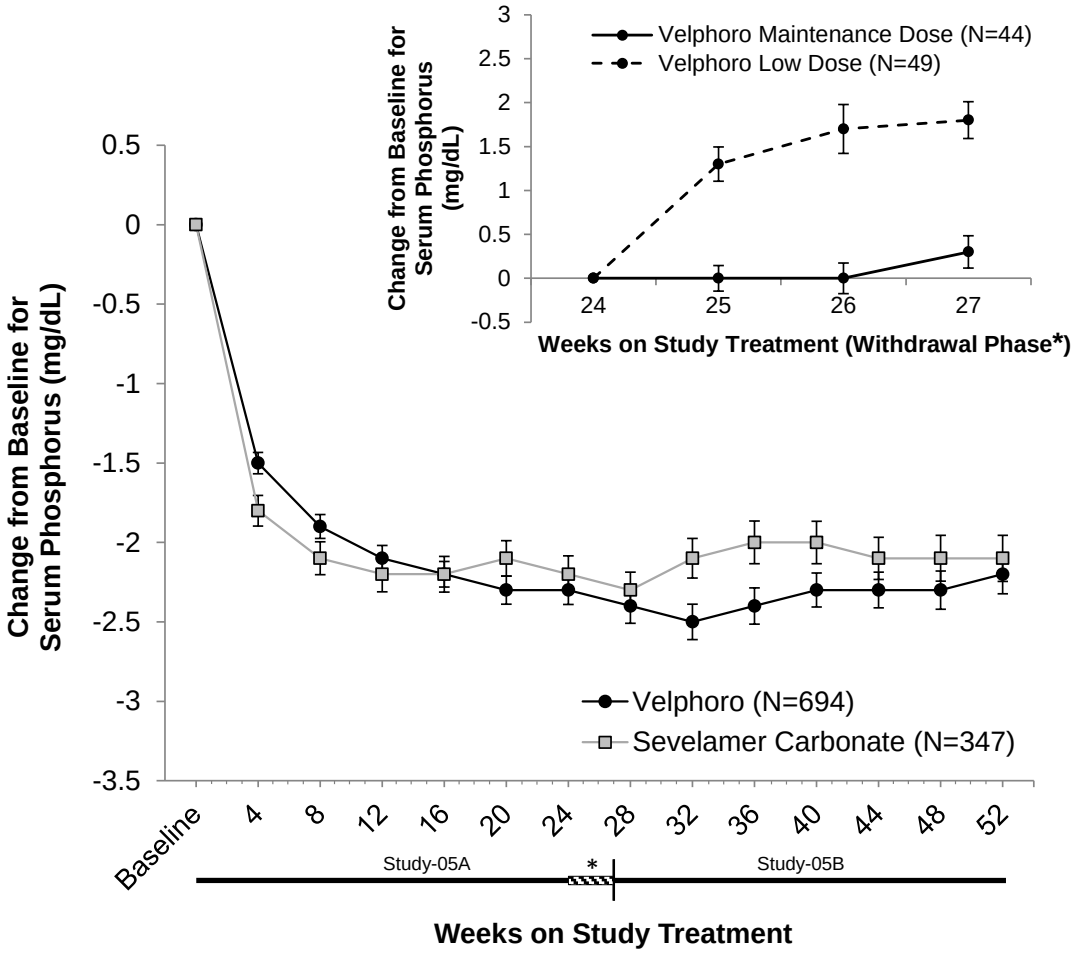

Figure 1 Mean change (±SEM) from baseline in serum phosphorus over time in Study‑05A and extension Study‑05B. Insert showing the mean change (±SEM) from baseline in serum phosphorus during the withdrawal phase of the study (Weeks 24 to 27) for Velphoro non-effective low dose control (250 mg /day) versus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

Age, gender, race, or dialysis modality did not affect the efficacy of Velphoro.

There were no clinically meaningful changes for serum iron, ferritin, TSAT levels, vitamins (A, D, E and K) with Velphoro. There was no evidence of accumulation of iron during one year treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

Velphoro are chewable tablets supplied as brown, circular, bi-planar tablets, embossed with “PA 500” on 1 side. Each tablet of Velphoro contains 500 mg iron as sucroferric oxyhydroxide. Velphoro chewable tablets are packaged as follows:

NDC 49230-645-51 Bottle of 90 chewable tablets

Storage

Keep the bottle tightly closed in order to protect from moisture.

Store at 25°C (77°F) with excursions permitted to 15 to 30°C (59 to 86°F).

17 PATIENT COUNSELING INFORMATION

Inform patients that Velphoro chewable tablets should be chewed or crushed. Do not swallow whole. *[see Dosage and Administration (2)]*.

Velphoro should be taken with meals.

Instruct patients on concomitant medications that should be dosed apart from Velphoro *[see Drug Interactions. (7)]*

Inform patients that Velphoro can cause discolored (black) stool, but this discoloration of the stool is considered normal with oral medications containing iron.

Inform patients that Velphoro can stain teeth.

Inform patients to report any rash to their health care professional.

Distributed by:

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