

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® (sucroferic 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

- Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, tablets may be crushed. (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 (sucroferic 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 doxycycline at least 1 hour before Velphoro. (7)
- Velphoro should not be prescribed with oral levothyroxine. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2014

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

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

5

6 **2 DOSAGE AND ADMINISTRATION**

7 Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and
8 swallowing, the tablets may be crushed.

9 *Starting Dose*

10 The recommended starting dose of Velphoro is 3 tablets (1,500 mg) per day,
11 administered as 1 tablet (500 mg) 3 times daily with meals.

12 *Titration and Maintenance*

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

17 Based on clinical studies, on average patients required 3 to 4 tablets (1,500 mg to
18 2,000 mg) a day to control serum phosphorus levels.

19 The highest daily dose studied in a Phase 3 clinical trial in ESRD patients was
20 6 tablets (3,000 mg) per day.

21 *Administration*

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

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

27

28 **3 DOSAGE FORMS AND STRENGTHS**

29 Velphoro (sucroferric oxyhydroxide) chewable tablet 500 mg.

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

32

33 **4 CONTRAINDICATIONS**

34 None.

35

36 **5 WARNINGS AND PRECAUTIONS**

37 **5.1 Monitoring in Patients with Gastrointestinal Disorders or Iron** 38 **Accumulation Disorders**

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

43

44 **6 ADVERSE REACTIONS**

45 **6.1 Clinical Trial Experience**

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

50 The safety data derived from Velphoro clinical trials reflect exposure to Velphoro in
51 2 active-controlled clinical studies involving a total of 778 patients on hemodialysis
52 and 57 patients on peritoneal dialysis exposed for up to 55 weeks. Dosage regimens
53 ranged from 250 mg to 3,000 mg per day.

54 As expected with oral preparations containing iron, discolored (dark colored) feces
55 was a commonly occurring adverse drug reaction.

56 In a parallel design, dose-finding study of Velphoro with a treatment duration of
57 6 weeks in hemodialysis patients, adverse reactions for Velphoro (N=128) were
58 similar to those reported for the active-control group (sevelamer hydrochloride)
59 (N=26), with the exception of discolored feces (12%) which did not occur in the
60 active-control group and diarrhea (6%).

61 In a 55-week, open-label, active-controlled, parallel design, safety and efficacy study
62 involving 968 hemodialysis patients and 86 peritoneal dialysis patients treated with
63 either Velphoro (N=707 including 57 peritoneal dialysis patients) or the active-control
64 (sevelamer carbonate) (N=348 including 29 peritoneal dialysis patients), adverse

65 reactions occurring in more than 5% in the Velphoro group were diarrhea (24%),
 66 discolored feces (16%), and nausea (10%). The majority of diarrhea events in the
 67 Velphoro group were mild and transient, occurring soon after initiation of treatment,
 68 and resolving with continued treatment. Similar adverse reactions occurred at similar
 69 rates in hemodialysis and peritoneal dialysis patients. The most common adverse
 70 reactions (>1%) leading to withdrawal were diarrhea (4%), product taste abnormal
 71 (2%), and nausea (2%).

72

73 **7 DRUG INTERACTIONS**

74

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	Take at least 1 hour before Velphoro.
Oral drugs that should not be prescribed with Velphoro	
Levothyroxine	

75

76 *Oral medications not listed in Table 1*

77 There are no empirical data on avoiding drug interactions between Velphoro and most
 78 concomitant oral drugs. For oral medications where a reduction in the bioavailability

79 of that medication would have a clinically significant effect on its safety or efficacy,
80 consider separating the administration of the two drugs. The necessary separation
81 depends upon the absorption characteristics of the medication concomitantly
82 administered, such as the time to reach peak systemic levels and whether the drug is
83 an immediate release or an extended release product. Where possible, consider
84 monitoring for clinical response and/or blood levels of concomitant medications that
85 have a narrow therapeutic range.

86

87 **8 USE IN SPECIFIC POPULATIONS**

88 **8.1 Pregnancy**

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

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

97 **8.2 Labor and Delivery**

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

101 **8.3 Nursing Mothers**

102 Since the absorption of iron from Velphoro is minimal [see *Clinical Pharmacology*
103 *(12.3)*], excretion of Velphoro in breast milk is unlikely.

104 **8.4 Pediatric Use**

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

106 **8.5 Geriatric Use**

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

110

111 **10 OVERDOSAGE**

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

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

117

118 **11 DESCRIPTION**

119 Velphoro chewable tablets are brown, circular, bi-planar, and are embossed with
120 “PA 500” on 1 side. Each tablet of Velphoro contains 500 mg iron (in 2,500 mg
121 sucroferric oxyhydroxide). The Velphoro drug substance is a mixture of polynuclear
122 iron(III)-oxyhydroxide, sucrose, and starches. The active moiety, polynuclear
123 iron(III)-oxyhydroxide, is practically insoluble and cannot be absorbed. The inactive
124 ingredients are woodberry flavor, neohesperidin dihydrochalcone, magnesium
125 stearate, and silica (colloidal, anhydrous).

126

127 **12 CLINICAL PHARMACOLOGY**

128 **12.1 Mechanism of Action**

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

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

134 **12.2 Pharmacodynamics**

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

139 **12.3 Pharmacokinetics**

140 The active moiety of Velphoro, polynuclear iron(III)-oxyhydroxide (pn-FeOOH), is
141 practically insoluble and therefore not absorbed and not metabolized. Its degradation
142 product, mononuclear iron species, can however be released from the surface of
143 pn-FeOOH and be absorbed.

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

146 The sucrose and starch components of Velphoro can be digested to glucose and
147 fructose, and maltose and glucose, respectively. These compounds can be absorbed in
148 the blood. One tablet is equivalent to 1.4 g of carbohydrates.

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

155 *Drug Interaction Studies*

156 *In vitro*

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

161 Interaction with Velphoro was seen with the following drugs: alendronate,
162 doxycycline, levothyroxine, and paricalcitol.

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

165 *In vivo*

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

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

174

175 **13 NONCLINICAL TOXICOLOGY**

176 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

177 Carcinogenicity studies were performed in mice and rats.

178 In the 2-year carcinogenicity study in mice, animals were given Velphoro by diet at
179 doses of 250, 500 or 1,000 mg/kg/day. Rare but not statistically significant neoplastic
180 adenocarcinomas were seen in the colon of male mice at doses of 500 and
181 1,000 mg/kg/day. For a 60 kg person, the no-observed-adverse-effect level (NOAEL)
182 of 250 mg/kg/day represents 5 times (on a body weight basis) the maximum
183 recommended clinical dose of 3,000 mg/day. In addition, an increased incidence of
184 epithelial hyperplasia was seen in the colon at all dosage levels (i.e., ≥ 5 times the
185 maximum recommended clinical dose) and in the cecum at the highest dosage
186 (equivalent to 20 times the maximum recommended clinical dose). The development
187 of adenocarcinoma in the male mice was considered not a genotoxic effect, but the
188 result of chronic local irritation from high amounts of intraluminal Velphoro in the GI
189 tract.

190 In the 2-year rat carcinogenicity study, animals were given Velphoro by diet at doses
191 of 40, 150 or 500 mg/kg/day. No statistically significantly increased incidences of
192 tumors were found, but there were increased incidences in epithelial hyperplasia with
193 or without submucosal inflammation in duodenum, cecum and colon at the dose of
194 500 mg/kg/day (10 times the maximum recommended clinical dose).

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

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

200 **13.2 Animal Toxicity and/or Pharmacology**

201 In pregnant rats given up to 800 mg/kg/day Velphoro by oral gavage from Days 6 to
202 17 post-mating, no embryo-fetal development toxicity was observed. This dose
203 corresponds to 16 times the maximum recommended clinical dose.

204 In pregnant rabbits given 50, 100 or 200 mg/kg/day Velphoro by oral gavage, from
205 Days 6 to 19 post-mating, the number of fetuses with incomplete/unossified epiphyses
206 and metacarpals/phalanges was increased at the highest dose (corresponding to
207 4 times the recommended maximum clinical dose). Litter parameters were not
208 adversely affected.

209 In pregnant rats given Velphoro at 100, 280, or 800 mg/kg/day by oral gavage from
210 Day 6 post-mating to lactation Day 20, offspring body weight gain was lower at age

211 5-13 weeks and neuromuscular function was delayed at the dose of 800 mg/kg/day.
212 This dose represented 16 times the maximum recommended clinical dose.

213

214 **14 CLINICAL STUDIES**

215 The ability of Velphoro to lower serum phosphorus in ESRD patients on dialysis was
216 demonstrated in 2 randomized clinical trials: one 6-week, open-label,
217 active-controlled (sevelamer hydrochloride), dose-finding study; and one 55-week,
218 open-label, active-controlled (sevelamer carbonate), parallel-group, safety and
219 efficacy study.

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

223 **14.1 Fixed-dose Study**

224 In Study-03A, 154 ESRD patients on hemodialysis who were hyperphosphatemic
225 (serum phosphorus >5.5 mg/dL but <7.75 mg/dL) following a 2-week phosphate
226 binder washout period, were randomized to receive Velphoro at 250 mg/day,
227 1,000 mg/day, 1,500 mg/day, 2,000 mg/day, or 2,500 mg/day or active-control
228 (sevelamer hydrochloride). Velphoro treatment was divided across meals, depending
229 on dose. No dose titration was allowed. Within each of the groups, the serum
230 phosphorus level at the end of treatment was compared to baseline value. Velphoro
231 was shown to be efficacious ($p \leq 0.016$) for all doses except 250 mg/day. There were
232 no patient-reported dose limiting treatment-emergent adverse events.

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

238 **14.2 Dose Titration Study**

239 In Study-05A, 1,054 patients on hemodialysis (N=968) or peritoneal dialysis (N=87)
240 with serum phosphorus ≥ 6 mg/dL following a 2-4 week phosphate binder washout
241 period, were randomized and treated with either Velphoro, at a starting dose of
242 1,000 mg/day (N=707), or active-control (sevelamer carbonate, N=348) for 24 weeks.
243 At the end of Week 24, 93 patients on hemodialysis whose serum phosphorus levels
244 were controlled (<5.5 mg/dL) with Velphoro in the first part of the study, were
245 re-randomized to continue treatment with either their Week 24 maintenance dose
246 (N=44 or a non-effective low dose control 250 mg/day, N=49) of Velphoro for a
247 further 3 weeks. At Week 27, a superiority analysis of the Velphoro maintenance dose

248 versus low dose was performed. The maximum dose of Velphoro was 3,000 mg/day
 249 (6 tablets/day) and the minimum dose was 1,000 mg/day (2 tablets/day). Velphoro
 250 was administered with food and the daily dose was divided across the largest meals of
 251 the day.

252 The Velphoro maintenance dose (1,000 to 3,000 mg/day) was statistically
 253 significantly superior in sustaining the phosphorus lowering effect in hemodialysis
 254 patients at Week 27 (p<0.001) compared with the non-effective low dose control. The
 255 results are provided in Table 2.

256 **Table 2 Mean (SD) Serum Phosphorus and Change from Baseline to End**
 257 **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)

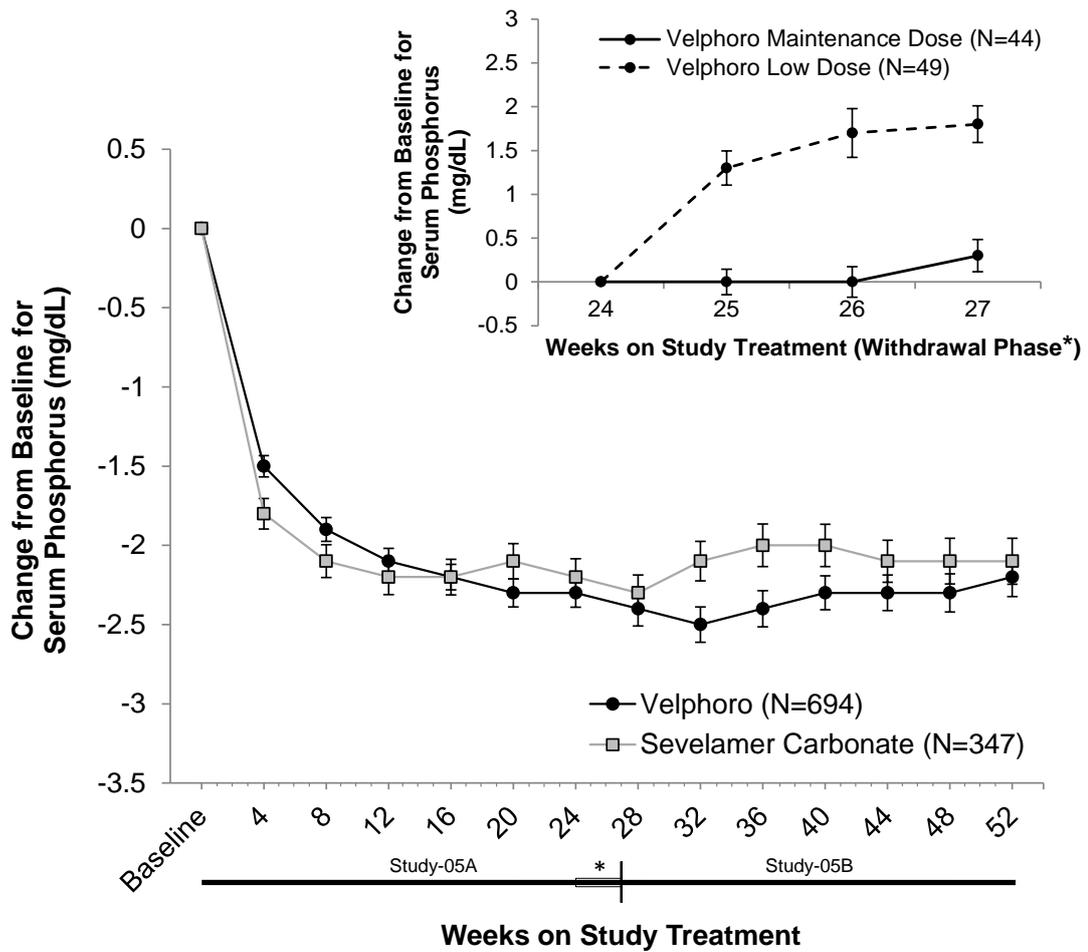
258 * p<0.001 for the difference in least square means of the change from BL to Week 27/End of Treatment (LOCF principle)
 259 between Velphoro maintenance dose and low dose using a covariance analysis (MIXED Model).
 260 Notes: BL is Week 24 or latest value available before Week 24 when Week 24 result is missing; End of Treatment is Week 27
 261 value or includes the latest evaluable measurement after Week 24 (i.e., LOCF).
 262 BL = Baseline; LOCF = Last observation carried forward; SD = Standard deviation.
 263

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

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

272 Serum iron level increases from baseline were not clinically meaningful and did not
 273 differ significantly compared to the active control. There was no evidence of
 274 accumulation of iron during one year treatment.

275 There were no clinically meaningful changes for vitamins (A, D, E and K) with
 276 Velphoro.



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 278
 279
 280
 281
 282
 283

Figure 1 Mean change (\pm SEM) from baseline in serum phosphorus over time in Study-05A and extension Study-05B. Insert showing the mean change (\pm 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.

284 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

288 NDC 49230-645-51 Bottle of 90 chewable tablets

289 **Storage**

290 Store in the original package and keep the bottle tightly closed in order to protect
291 from moisture.

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

293

294 **17 PATIENT COUNSELING INFORMATION**

295 Inform patients that Velphoro tablets must be chewed and not swallowed whole. To
296 aid with chewing and swallowing, the tablets may be crushed [*see Dosage and*
297 *Administration (2)*].

298 Velphoro should be taken with meals.

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

301 Inform patients that Velphoro can cause discolored (black) stool.

302

303 Distributed by:

304 Fresenius Medical Care North America
305 920 Winter Street
306 Waltham, MA 02451

307 US Patent Nos. 6174442 and pending, comparable and/or related patents.

308

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