

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

- 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 (less than or equal to 5.5 mg/dL) 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 (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Velphoro can be administered concomitantly with ciprofloxacin, digoxin, enalapril, furosemide, HMG-CoA reductase inhibitors, hydrochlorothiazide, losartan, metformin, metoprolol, nifedipine, omeprazole, quinidine and warfarin. (7)
- Take alendronate and doxycycline at least 1 hour before Velphoro. (7)
- Velphoro should not be prescribed with oral levothyroxine and oral vitamin D analogs. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2013

Comment [AJP2]: Need to add phone number and web address

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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
4 of 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 Serum phosphorus levels should be monitored and the dose of Velphoro titrated in
14 decrements or increments of 500 mg (1 tablet) per day as needed until an acceptable
15 serum phosphorus level (less than or equal to 5.5 mg/dL) is reached, with regular
16 monitoring afterwards. Titration can be started as early as 1 week after treatment
17 initiation and adjusted at weekly intervals thereafter if necessary.

18 Based on clinical studies, on average patients required 3 to 4 tablets (1,500 mg to
19 2,000 mg) a day to control serum phosphorus levels.

20 The highest daily dose studied in a Phase 3 clinical trial in ESRD patients was
21 6 tablets (3,000 mg) per day.

22 *Administration*

23 Velphoro must be administered with meals. To maximize the dietary phosphate
24 binding, the total daily dose should be divided across the meals of the day. No
25 additional fluid above the amount usually taken by the patient is required.

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

28

29 **3 DOSAGE FORMS AND STRENGTHS**

30 Velphoro (sucroferric oxyhydroxide) chewable tablet 500 mg.

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

33

34 **4 CONTRAINDICATIONS**

35 None.

36

37 **5 WARNINGS AND PRECAUTIONS**

38 **5.1 Monitoring in Patients with Gastrointestinal Disorders or Iron** 39 **Accumulation Disorders**

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

44

45 **6 ADVERSE REACTIONS**

46 **6.1 Clinical Trial Experience**

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

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

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

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

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

66 reactions occurring more than 5% in the Velphoro group were diarrhea (24%),
67 discolored feces (16%), and nausea (10%). The majority of diarrhea events in the
68 Velphoro group were mild and transient, occurring soon after initiation of treatment,
69 and resolving with continued treatment. Similar adverse reactions occurred at similar
70 rates in hemodialysis and peritoneal dialysis patients. The most common adverse
71 reactions (>1%) leading to withdrawal were diarrhea (4%), product taste abnormal
72 (2%), and nausea (2%).

73

74 **7 DRUG INTERACTIONS**

Drugs that can be administered concomitantly with Velphoro	
Ciprofloxacin Digoxin Enalapril Furosemide HMG-CoA reductase inhibitors Hydrochlorothiazide Losartan Metformin Metoprolol Nifedipine Omeprazole Quinidine Warfarin	
Drugs that are to be separated from Velphoro and meals	
Dosing Recommendations	
Alendronate Doxycycline	Take these at least 1 hour before Velphoro.
Oral drugs that should not be prescribed with Velphoro	
Levothyroxine Vitamin D analogs	

75 **8 USE IN SPECIFIC POPULATIONS**

76 **8.1 Pregnancy**

77 Pregnancy Category B: Reproduction studies have been performed in rats and rabbits
78 at doses up to 16 and 4 times, respectively, the human maximum recommended
79 clinical dose on a body weight basis, and have not revealed evidence of impaired
80 fertility or harm to the fetus due to Velphoro [see *Nonclinical Toxicology (13.2)*].
81 However, Velphoro at a dose up to 16 times the maximum clinical dose was
82 associated with an increase in post-implantation loss in pregnant rats. Because animal
83 reproduction studies are not always predictive of human response, this drug should be
84 used during pregnancy only if clearly needed.

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

86 **8.2 Labor and Delivery**

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

90 **8.3 Nursing Mothers**

91 Since the absorption of iron from Velphoro is minimal [see *Clinical Pharmacology*
92 (12.3)], excretion of Velphoro in breast milk is unlikely.

93 **8.4 Pediatric Use**

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

95 **8.5 Geriatric Use**

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

99

100 **10 OVERDOSAGE**

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

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

106

107 **11 DESCRIPTION**

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

115

116 **12 CLINICAL PHARMACOLOGY**

117 **12.1 Mechanism of Action**

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

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

123 **12.2 Pharmacodynamics**

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

128 **12.3 Pharmacokinetics**

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

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

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

138 The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day, was
139 investigated in 16 chronic kidney disease patients (8 pre-dialysis and 8 hemodialysis
140 patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L). In

141 healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on
142 Day 21. In chronic kidney disease patients, the median uptake was much less, 0.04%
143 on Day 21.

144 *Drug Interaction Studies*

145 *In vitro*

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

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

152 Following drugs did not show interaction with Velphoro: ciprofloxacin, enalapril,
153 hydrochlorothiazide, metformin, metoprolol, nifedipine, and quinidine.

154 *In vivo*

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

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

162

163 **13 NONCLINICAL TOXICOLOGY**

164 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

165 Carcinogenicity studies were performed in mice and rats.

166 In the 2-year carcinogenicity study in mice, animals were given Velphoro by diet at
167 doses of 250, 500 or 1,000 mg/kg/day. Rare but not statistically significant neoplastic
168 adenocarcinomas were seen in the colon of male mice at doses of 500 and
169 1,000 mg/kg/day. For a 60 kg person, the no-observed-adverse-effect level (NOAEL)
170 of 250 mg/kg/day represents 5 times (on a body weight basis) the maximum
171 recommended clinical dose of 3,000 mg/day. In addition, an increased incidence of
172 epithelial hyperplasia was seen in the colon at all dosage levels (i.e., ≥ 5 times the
173 maximum recommended clinical dose) and in the cecum at the highest dosage
174 (equivalent to 20 times the maximum recommended clinical dose). The development

175 of adenocarcinoma in the male mice was considered not a genotoxic effect, but the
176 result of chronic local irritation from high amounts of intraluminal Velphoro in the GI
177 tract.

178 In the 2-year rat carcinogenicity study, animals were given Velphoro by diet at doses
179 of 40, 150 or 500 mg/kg/day. No statistically significantly increased incidences of
180 tumors were found, but there were increased incidences in epithelial hyperplasia with
181 or without submucosal inflammation in duodenum, cecum and colon at the dose of
182 500 mg/kg/day (10 times the maximum recommended clinical dose).

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

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

188 **13.2 Animal Toxicity and/or Pharmacology**

189 In pregnant rats given up to 800 mg/kg/day Velphoro by oral gavage from Days 6 to
190 17 post-mating, no embryo-fetal development toxicity was observed. This dose
191 corresponds to 16 times the maximum recommended clinical dose.

192 In pregnant rabbits given 50, 100 or 200 mg/kg/day Velphoro by oral gavage, from
193 Days 6 to 19 post-mating, the number of fetuses with incomplete/unossified epiphyses
194 and metacarpals/phalanges was increased at the highest dose (corresponding to
195 4 times the recommended maximum clinical dose). Litter parameters were not
196 adversely affected.

197 In pregnant rats given Velphoro at 100, 280, or 800 mg/kg/day by oral gavage from
198 Day 6 post mating to lactation Day 20, offspring body weight gain was lower at age
199 5-13 weeks and neuromuscular function was delayed at the dose of 800 mg/kg/day.
200 This dose represented 16 times the maximum recommended clinical dose.

201

202 **14 CLINICAL STUDIES**

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

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

211 **14.1 Fixed-dose Study**

212 In Study-03A, 154 ESRD patients on hemodialysis who were hyperphosphatemic
213 (serum phosphorus >5.5 mg/dL but <7.75 mg/dL) following a 2-week phosphate
214 binder washout period, were randomized to receive Velphoro at 250 mg/day,
215 1,000 mg/day, 1,500 mg/day, 2,000 mg/day, or 2,500 mg/day or active-control
216 (sevelamer hydrochloride). Velphoro treatment was divided across meals, depending
217 on dose. No dose titration was allowed. Within each of the groups, the serum
218 phosphorus level at the end of treatment was compared to baseline value. Velphoro
219 was shown to be efficacious ($p \leq 0.016$) for all doses except 250 mg/day. There were
220 no patient-reported dose limiting treatment-emergent adverse events.

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

226 **14.2 Dose Titration Study**

227 In Study-05A, 1,054 patients on hemodialysis (N=968) or peritoneal dialysis (N=87)
228 with serum phosphorus ≥ 6 mg/dL following a 2-4 week phosphate binder washout
229 period, were randomized and treated with either Velphoro, at a starting dose of
230 1,000 mg/day (N=707), or active-control (sevelamer carbonate, N=348) for 24 weeks.
231 At the end of Week 24, 93 patients on hemodialysis whose serum phosphorus levels
232 were controlled (<5.5 mg/dL) with Velphoro in the first part of the study, were
233 re-randomized to continue treatment with either their Week 24 maintenance dose
234 (N=44 or a non-effective low dose control 250 mg/day, N=49) of Velphoro for a
235 further 3 weeks. At Week 27, a superiority analysis of the Velphoro maintenance dose
236 versus low dose was performed. The maximum dose of Velphoro was 3,000 mg/day
237 (6 tablets/day) and the minimum dose was 1,000 mg/day (2 tablets/day). Velphoro
238 was administered with food and the daily dose was divided across the largest meals of
239 the day.

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

244 **Table 1 Mean (SD) Serum Phosphorus and Change from Baseline to End**
245 **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)

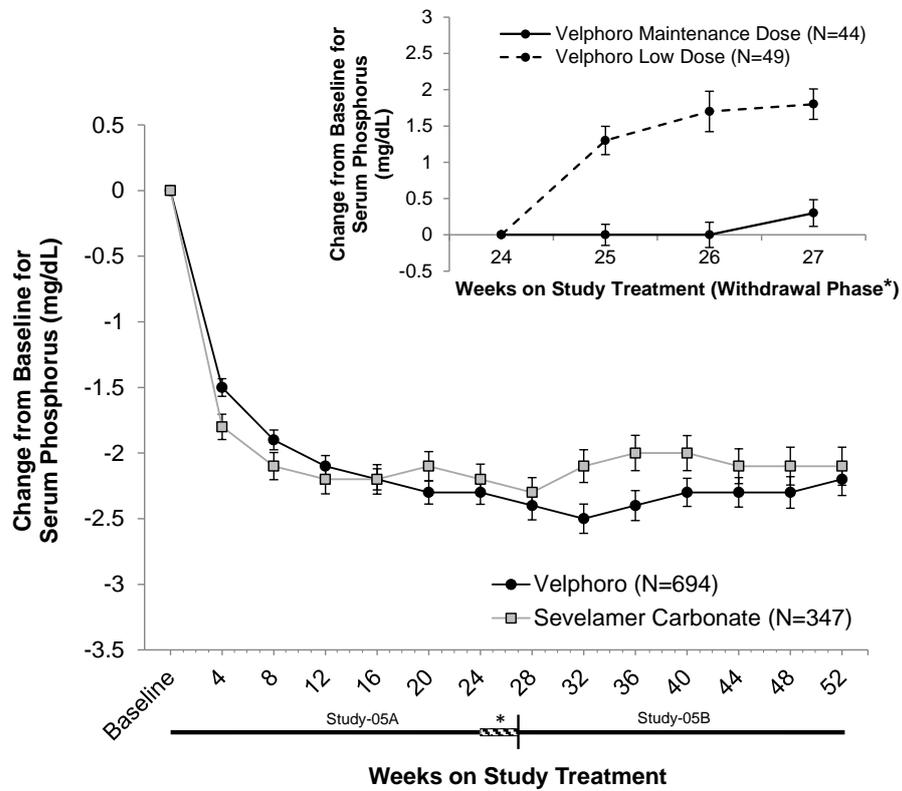
246 * p<0.001 for the difference in least square means of the change from BL to Week 27/End of Treatment (LOCF principle)
247 between Velphoro maintenance dose and low dose using a covariance analysis (MIXED Model).
248 Notes: BL is Week 24 or latest value available before Week 24 when Week 24 result is missing; End of Treatment is Week 27
249 value or includes the latest evaluable measurement after Week 24 (i.e., LOCF).
250 BL = Baseline; LOCF = Last observation carried forward; SD = Standard deviation.
251

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

256 Serum phosphorus levels declined rapidly during the first few weeks of treatment and
257 remained relatively constant thereafter. The phosphorus lowering effect of Velphoro
258 was consistently maintained through 12 months of treatment (shown in Figure1).Age,
259 gender, race, or dialysis modality did not affect the efficacy of Velphoro.

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

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



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 268
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 271

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.

272 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

277 **Storage**

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

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

281

282 **17 PATIENT COUNSELING INFORMATION**

283 • **Dosing Recommendations**

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

287 Velphoro should be taken with meals.

288 | Some drugs need to be given at least one hour before Velphoro [*see Drug*
289 *Interactions. (7)*]

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290 • **Adverse Reactions**

291 Velphoro can cause discolored (black) stool. Discolored (black) stool may mask GI
292 bleeding. Velphoro does not affect guaiac based (Hämocult) or immunological based
293 (iColo Rectal, and Hexagon Opti) fecal occult blood tests.

294

295 Distributed by:

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299

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