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APPLICATION NUMBER:

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SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	November, 2013
From	Shen Xiao, M.D., PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205-109
Applicant	Vifor Fresenius Medical Care Inc.
Date of Submission	February 1, 2013
PDUFA Goal Date	December 1, 2013
Proprietary Name / Established (USAN) names	Velphoro™ (sucroferric oxyhydroxide)
Dosage forms / Strength	Chewable Tablet/500 mg per tablet
Proposed Indication(s)	Control of serum phosphorus in patients with end stage renal disease (ESRD)
Recommended:	Approval

This secondary review is based on the primary reviews of:

- DMEPA: Kim DeFronzo, 10/05/2013
- OSI: Kassa Ayalew, 10/11/2013
- Biopharmaceutics: Elsbeth Chikhale, 09/29/2013
- CMC: Thomas Wong, 9/27/2013
- Pharmacology/Toxicology: Baichun Yang, 04/25/2013
- Clinical Pharmacology: Ju-Ping Lai, 10/22/2013
- Biometrics: Ququan Liu, 09/21/2013
- Clinical: Shen Xiao, 10/11/2013

1. Introduction

Velphoro [redacted] (b) (4), PA21) is an iron-based phosphate binder. The proposed indication is for the control of serum phosphorus levels in patients with end stage renal disease (ESRD) on chronic hemodialysis or peritoneal dialysis therapy. The members of the primary review team agree that the product should be approved pending agreement with the applicant on labeling. This CDTL review elaborates on the rationale for recommending approval of this product. In addition to addressing data on efficacy, safety and drug-drug interactions, this review will discuss issues highlighted in the (1) biopharmaceutical and CMC reviews related to dissolution and stability and (2) pharmacology/toxicology review related to carcinogenicity findings in the GI tract.

2. Background

Several phosphate binders have been approved and are currently used for the control of serum phosphorus levels in patients with ESRD on chronic dialysis. These phosphate binders include calcium based, lanthanum based, and anion-exchange resin products. Velphoro is the first iron-

based phosphate binder. Use of this product in patients on chronic dialysis may allow patients to avoid some specific adverse events associated with the use of other approved phosphate binders such as hypercalcemia, bone deposition, certain types of GI events, and possibly lessen the pill burden.

It is well known that iron compounds have phosphate adsorption properties. However, oxidic iron compounds like Fe_2O_3 have a rather low phosphate adsorption capacity, whereas soluble iron complexes have the disadvantage of being absorbed in the intestine. The iron (III)-oxyhydroxide of Velphoro™ powder is practically insoluble and possesses a high phosphate adsorption capacity in combination with a low iron release.

3. CMC

Both the CMC reviewer, Dr.Thomas Wong, and biopharmaceutics reviewer, Dr. Elsbeth Chikhale, recommend approval of this product.

There was initial concern about the proposed dissolution specifications for the product. Dr. Chikhale felt that based on the discriminating capability of the dissolution method and the overall dissolution data from the clinical and registration batches, the proposed acceptance criterion of Q= (b) (4) at 45 minutes might not be acceptable and a dissolution acceptance criterion of Q= (b) (4) at 30 minutes was recommended for this product. However, she also agreed that the applicant could have a wider dissolution acceptance criterion for their product if the results from in vitro phosphate adsorption/binding studies comparing an old failed batch (>30 months stability) of drug product with a slower dissolution rate vs. a new acceptable fresh batch of drug product with a faster dissolution rate, demonstrated that the phosphate adsorption and binding between these products were equivalent.

The applicant submitted their *in vitro* phosphate adsorption/binding data on October 16, 2013. Based on this submission, Dr. Chikhale agreed that the provided data support the approval of the originally proposed dissolution acceptance criterion of Q= (b) (4) at 45 minutes.

Overview of drug substance and drug product (from CMC review)
Drug Substance (s): Sucroferric oxyhydroxide is a complex which consists of the polynuclear iron (III)-oxyhydroxide, sucrose and starch. The pn-FeOOH moiety is produced as an aqueous suspension, it is chemically not stable and cannot be isolated and stored as an active pharmaceutical ingredient. (b) (4)

Polynuclear iron (III)-oxyhydroxide is a phosphate binder and exhibits minimal release of iron across the range of pH values found in the GI tract. It adsorbs the dietary phosphate in the GI tract, preventing its uptake into the blood, and thereby reducing the serum level of phosphorus. The phosphate bound to polynuclear iron (III)-oxyhydroxide is subsequently eliminated in the feces. The polynuclear iron (III)-oxyhydroxide is prepared by (b) (4)

(b) (4) a commercial batch size for PA21 ranging between (b) (4) is proposed. The applicant provided adequate information regarding structure elucidation. Available 48 months stability data at both 25°C/60% RH and 30°C/75% RH storage conditions supports a (b) (4) re-test dating when stored at 30°C/65% RH and packaged into (b) (4)

Drug Product: The drug product is a chewable tablet. The tablets are red-brown, round, flat-faced chewable tablet embossed with "PA 500" and is approximately (b) (4) Each tablet contains 500 mg elemental iron equivalent to 2500 mg sucroferric oxyhydroxide complex and the following excipients: woodberry flavor, neohesperidin dihydrochalcone, magnesium stearate, and silica. The tablets will be manufactured by Vifor SA in Switzerland and by (b) (4) in Germany. Commercial batch size for the Vifor and (b) (4) facility is (b) (4) tablets and (b) (4) tablets, respectively. Tablets are packaged in HDPE bottles with 30 counts and 90 counts per bottle. (b) (4) Tablets are stored at 25ºC (77ºF). Excursions are permitted between 15°C and 30°C (59°F and 86°F). Available 18 months stability data supports a 30-month expiration dating period for the tablets when packaged in the proposed commercial packages and stored in the aforementioned storage conditions.

Facilities review/inspection:
Three sites have been inspected by the Office of Compliance. According to the CDER EES report, all were found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer, Dr. Baichun Yang, recommends approval of this product. The only outstanding issue relates to the description of a positive mouse carcinogenicity finding in labeling.

In a mouse carcinogenicity study, treatment-related neoplastic adenocarcinomas were observed in mouse colon and cecum with all drug groups. This finding, however, was not observed in dogs in the general toxicity study. Therefore, the applicant asserted that (b) (4) The reviewer, Dr. Yang, disagreed with this assertion. Potential chronic GI irritation, inflammation, and/or hyperplasia caused by the product could be risk factors for the development of GI cancer in humans. There were also dose-related increases in the incidence and/or severity of GI epithelial hyperplasia in mice and an increased incidence of GI epithelial/mucosal hyperplasia in rats. Hence, Dr. Yang suggested that (b) (4)

(b) (4)

Dr. Maronpot re-examined the mouse large intestinal lesions in the carcinogenicity study, and re-classified the mouse intestinal lesions as shown in the table below. (b) (4)

PA21 Dose (mg Fe/kg/day)	Males				Females			
	Control	250	500	1,000	Control	250	500	1,000
Colon								
No. examined	57	60	57	60	59	58	57	60
Adenocarcinoma[1]	0 (1)	0 (3)	3 (5)	1 (9)	0	0	0	0 (3)
Mucosal diverticulum/ cysts/hyperplasia	2	1	3	6	0	0	2	4
Cecum								
No. examined	51	58	50	54	57	54	55	59
Adenocarcinoma[1]	0	0 (1)	0 (2)	0 (1)	0	0 (1)	0	0
Adenoma	0	0	0	1	0	0	0	0
Mucosal diverticulum/ cysts/hyperplasia	0	3	4	12[2]	0	0	0	3

1 Incidence values based on original classification shown in parentheses.
2 $p<0.01$

Dr. Yang consulted with an FDA veterinary pathologist, Dr. Luann Mckinney. Dr. Mckinney felt that the cecal adenocarcinomas in Dr. Maronpot's classification were consistent with literature descriptions of adenocarcinoma and were diagnostically straightforward, and agreed with Dr. Maronpot's re-classification of the mouse intestinal lesions. Therefore, in the carcinogenicity study in mice, NOAEL and LOAEL levels for adenocarcinoma were 250, and 500 mg iron/kg/day, representing 5 and 10 times (on a body weight basis), respectively, the maximum recommended clinical dose of 3,000 mg/day.

No new evidence was provided to support the assertion that large intestinal adenocarcinoma in mice is species-specific. Moreover, an increased incidence in epithelial hyperplasia with or without submucosal inflammation was seen in the duodenum, cecum and colon in rats, and a similar phosphate binding substance in another IND (b) (4) also caused large intestinal epithelial hyperplasia in monkeys. In fact, neither drug showed GI hyperplasia in the dog. Therefore, both the reviewer, Dr. Yang, and her team leader, Dr. Thomas Papoian, insist that (b) (4) Based on the aforementioned issues, I agree with Drs Yang and Papoian, the applicant has not provided adequate evidence to support the assertion that the adenocarcinoma finding is mouse-specific, and therefore, (b) (4)

5. Clinical Pharmacology

The clinical pharmacology review was conducted by Dr. Ju-Ping Lai with Dr. Dhananjay Marathe performing the Pharmacometric Review. Both of them recommend approval of this product provided an agreement can be reached on labeling related to drug-drug interactions.

Nine human study reports were submitted in support of dosing and the proposed claim, including 7 clinical pharmacology studies (5 *in vivo* DDI, 1 ADME and 1 PK studies), 2 phase II trials and 1 pivotal trial phase III trial. In addition, 22 *in vitro* studies were conducted to evaluate potential drug-drug interactions. Key clinical pharmacology findings are briefly described below (excerpted from the Clinical Pharmacology Review):

1. Following oral administration, the uptake of ^{59}Fe-PA21 was found to be < 0.1% in patients with chronic kidney disease (CKD) and 0.43% in healthy subjects supporting minimal absorption of iron from PA21.
2. Commonly used drugs in the target population were screened in an attempt to characterize the interaction potential in vitro. Among drugs studied, furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, and paricalcitol showed extensive binding with PA21 when incubated in an aqueous solution that mimics the conditions of the gastro-intestinal (GI) tract. The binding of levothyroxine, paricalcitol and atorvastatin to PA21 was less pronounced with the presence of phosphate.
3. Systemic exposure of losartan, furosemide, omeprazole, digoxin and warfarin were not altered when administered either concomitantly with PA21 or 2 hour after PA21 compared to testing of the drug alone.
4. Lipid-lowering effects of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors were not altered by PA21 over 52 weeks.
5. A trend towards a dose-dependent serum phosphorous lowering effect was observed although the relationship was relatively shallow over the range of 1000 mg iron/day to 2500 mg iron/day.
6. Near maximum serum phosphate lowering effects of PA21 were seen within 2 weeks with all doses that showed an effect.

The only outstanding issue at this time pertains to labeling for drug-drug interactions:

1. Both levothyroxine and paricalcitol showed a clear signal for binding in an *in vitro* study and lack *in vivo* information. The levothyroxin package insert (PI) states to separate dosing at least 4 hrs with iron products because of the formation of ferricthyroxine complex. However, this 4 hour separation is not practical with phosphate binders as they are typically given 3 times a day with food. (b) (4) [redacted] ince both drugs have parenteral forms available, the reviewer recommends administering Levothyroxine or Vitamin D analogs via non-oral route when taking these drugs with PA21 or considering the use of alternate oral phosphate binders.
2. Similarly, alendronate and doxycycline showed a clear signal for binding in an *in vitro* study but lack *in vivo* information. The PIs of these two products indicate that they should be taken in a fasted state if possible. Hence to be consistent with their PIs, the recommendation for these two drugs is to take them at least 1 hour before PA21.

For the reasons discussed above, I think the proposed labeling changes are reasonable.

6. Clinical Microbiology

There are no specific clinical microbiology issues in the current submission.

7. Clinical/Statistical- Efficacy

I conducted the Clinical Review and Dr. Liu conducted the Statistical Review. Both Dr. Liu and I recommend approval of this product.

Two studies, one phase 3 study (Study PA-CL-05A) and one phase 2 dose-ranging study (Study PA-CL-03A), provide the main support for efficacy. Study PA-CL-05B, a 28-week extension study to Study PA-CL-05A, mainly examined the safety and tolerability of Velphoro compared to sevelamer carbonate in patients on either HD or PD. However, data from this study were also used to evaluate long-term efficacy (changes from baseline to 12 months in serum phosphorus levels on Velphoro compared to sevelamer).

Study PA-CL-05A
Study PA-CL-05A was a 27-week, 2-stage re-randomization, withdrawal study with a 24-week randomized, open-label, active-controlled (sevelamer carbonate) first stage. The primary objective was to establish the superiority of Velphoro maintenance dose versus Velphoro low dose (non-effective dose) control in maintaining the phosphorus lowering effect in patients undergoing hemodialysis (HD), by comparing the change in serum phosphorus levels during a 3-week period (Stage 2) that followed 24 weeks of Velphoro treatment.

Adult ESRD subjects with serum phosphorus levels ≥6.0 mg/dL receiving chronic hemodialysis or peritoneal dialysis were enrolled in the study. After a 2-4 week washout period, eligible subjects were randomized and entered Stage 1.

Stage 1 was a prospective, randomized, parallel group, open-label, active controlled, 24-week study of Velphoro compared with sevelamer carbonate. In this stage, treatment of Velphoro or sevelamer was administered to 1,055 subjects (707 treated with Velphoro and 348 treated with sevelamer). The starting dose of Velphoro was 1000 mg/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 500 mg/day every 2 weeks were permitted. The maximum dose of Velphoro was 3000 mg/day (6 tablets/ day) and the minimum dose was 1000 mg (2 tablets/day). The starting dose of sevelamer carbonate (the active control) was 4.8 g/day. The dose of sevelamer was also titrated for efficacy and tolerability reasons; dose increases or decreases of 2.4 g/day (3 tablets/day) every 2 weeks were permitted. The maximum allowed dose of sevelamer carbonate was 14.4 g/day (18 tablets/day) and the minimum dose was 2.4 g/day (3 tablets/day). For subjects on HD, serum phosphorus was measured at weekly study visits for the first 8 weeks of treatment, then every 4 weeks until Week 24. For subjects on PD, serum phosphorus was measured every second week for the first 8 weeks of treatment, and then every 4 weeks until Week 24.

Stage 2, starting at Week 24, was a prospective, randomized, parallel group, open-label, 3-week comparison of Velphoro maintenance dose (MD) (dose previously titrated for efficacy and tolerability) versus Velphoro low dose (LD) control (fixed dose of 250 mg/day, a dose previously shown to be ineffective in the phase 2 dose finding study, Study PA-CL-03A). Ninety nine subjects on HD with controlled serum phosphorus level at Week 20 (according to the upper limit of the KDOQI target range <5.5 mg/dL) from the Stage 1 Velphoro treatment group were randomized 1:1 to either the Velphoro MD group (N=50) or LD control group (N=49). A superiority analysis was conducted for the change in serum phosphorus to Week 27 using Week 24 as a baseline. No dose adjustments were permitted during Weeks 24 to 27.

In stage 2 of the pivotal study, the mean serum phosphorus level in the low dose control group was significantly increased from baseline (36%) compared to an increase of 6% in the maintenance group (1.8 mg/dl vs. 0.3 mg/dl, P<0.001). The Week 24 maintenance dose (MD) of Velphoro (mean of 1480 mg/day) was superior (p<0.001) to the non effective low dose (LD) control (250 mg/day) in this 3-week withdrawal phase as shown in the table below.

Primary end point: Comparison of change in serum phosphorus levels from baseline to end of treatment in Stage 2 of Study PA-CL-05A (ITT population)

Time point	Serum phosphorus (mg/dl)		P value
	PA21 MD (n=44)	PA21 LD (n=49)	
Week 24 (baseline)	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	5.0±1.07	6.8±1.63	
Difference between baseline and Week 27	0.3±1.22	1.8±1.47	<0.001

(Medical reviewer table confirmed by statistician)

In stage 1 of the pivotal study, there was also a significant reduction from baseline in serum phosphorus levels in the Velphoro arm and this effect was maintained through Week 24. Effects on serum phosphorous were also similar in the Velphoro and sevelamer carbonate groups (39% vs. 34% reduction from baseline in serum phosphorus levels in the Velphoro and sevelamer arms, respectively).

Comparison of change in serum phosphorus levels from baseline to end of treatment in Stage 1 of Study PA-CL-05A

Time point	Serum phosphorus (mg/dl)	
	Velphoro (n=461)	Sevelamer (n=224)
Baseline (before the first dosing)	7.7±1.82	7.6±1.92
Week 12	5.5±1.32	5.2±1.29
Week 24	4.7±1.03	5.0±1.14
Difference between baseline and Week 24	3.0±1.91	2.6±2.07
P value	<0.01	<0.01

(Medical reviewer table confirmed by statistician)

Study PA-CL-03A

Study PA-CL-03A was a phase 2, 6-week open-label, randomized, active-controlled, dose-ranging study (250 to 2500 mg/day Velphoro) in ESRD patients on HD. The primary objective was to investigate the ability of different fixed doses of Velphoro to lower serum phosphorus levels in this population.

Adult ESRD subjects with serum phosphorus levels > 5.5 mg/dL receiving chronic hemodialysis were enrolled in the study. The study compared 5 fixed dosage regimens of Velphoro with a single dosage regimen of sevelamer hydrochloride. Subjects received Velphoro at 250 mg/day (N=26), 1000mg/day (N=26), 1500 mg/day (N=25), 2000 mg/day (N=27), or 2500 mg/day (N=24), or sevelamer hydrochloride at 4.8 g/day (N=26) for 6 weeks (42 days). No dose titration was allowed. Subjects were withdrawn if their serum phosphorus levels exceeded the upper safety limit of 8.5 mg/dL at any time as of 2 weeks after the start of treatment, or decreased below the lower safety limit of 3.5 mg/dL at any time after the start of treatment.

In this phase 2 dose-ranging study, except for the low dose group (250 mg/day), all Velphoro treatment groups and the sevelamer 4.8 g/day group showed a highly significant decrease in serum phosphorus levels from baseline to end of treatment. For the Velphoro dose groups, the decrease in serum phosphorus levels was generally dose dependent as shown in the table below.

Change in serum phosphorus from baseline in ESRD patients treated for 6 weeks in Study PA-CL-03A

Study Drug and Dose	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)							
	FAS[1]				PPS[2]			
	n	BL	Change From BL[3]	p-value[4] (Change From BL)	n	BL	Change From BL[3]	p-value[4] (Change From BL)
PA21 1.25 g/day	26	2.20 (6.82) [0.53 (1.64)]	-0.042 (-0.13) [0.65 (2.01)]	0.745	18	2.19 (6.77) [0.51 (1.57)]	0.07 (0.20) [0.65 (2.01)]	0.673
PA21 5.0 g/day	26	2.14 (6.61) [0.35 (1.08)]	-0.35 (-1.08) [0.68 (2.12)]	0.016	21	2.17 (6.72) [0.36 (1.10)]	-0.47 (-1.47) [0.65 (2.00)]	0.003
PA21 7.5 g/day	25	2.21 (6.85) [0.37 (1.15)]	-0.40 (-1.25) [0.39 (1.21)]	<0.001	22	2.20 (6.80) [0.39 (1.20)]	-0.41 (-1.26) [0.41 (1.27)]	<0.001
PA21 10.0 g/day	25	2.19 (6.77) [0.57 (1.75)]	-0.64 (-2.00) [0.55 (1.71)]	<0.001	20	2.17 (6.71) [0.58 (1.79)]	-0.64 (-1.97) [0.41 (1.28)]	<0.001
PA21 12.5 g/day	24	2.09 (6.47) [0.38 (1.19)]	-0.55 (-1.69) [0.58 (1.81)]	<0.001	19	2.07 (6.41) [0.34 (1.04)]	-0.57 (-1.77) [0.56 (1.74)]	<0.001
Sevelamer 4.8 g/day	24	2.24 (6.94) [0.52 (1.61)]	-0.34 (-1.06) [0.44 (1.35)]	<0.001	20	2.35 (7.28) [0.48 (1.49)]	-0.43 (-1.34) [0.40 (1.23)]	<0.001

1. All randomized subjects who received at least 1 dose of study treatment and had at least 1 post-BL efficacy evaluation (while on treatment – prior to follow-up evaluation) (N=150).
2. All randomized subjects that completed study per protocol (N=120).
3. Change from BL (Week 1, D1) to last value on treatment (Week 7, D1, or LOCF for missing values).
4. Single sample t-tests at 5% significance level, hierarchical procedure for PA21 dose groups (descending dose; no adjustment of alpha values).

Note: the list doses were in the total mass which equal 250 mg/day to 2500 mg/day PA 21(1.25 g/day to 12.5 g/day)
(Sponsor table from PA-CL-03A study report)

Other analyses

Responder analyses were also performed by determining the proportion of subjects with controlled serum phosphorus levels as defined by the Kidney Disease Outcomes Quality

Initiative (KDOQI) guidelines (3.5 to 5.5 mg/dL) in both PA-CL-03A and PA-CL-05A studies, and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2.5 to 4.5 mg/dL) in PA-CL-05A only. The results of these analyses were consistent with the primary efficacy endpoint findings. In PA-CL-03A, the proportion of subjects with "controlled" serum phosphorus levels at Week 7 (i.e., after 6 weeks of treatment) in the Velphoro 2500 mg/day group (60.0%) was greater than in the 250 mg/day LD group (21.1%). The proportion of subjects achieving this level of control in the sevelamer group (42.1%) was similar to the proportion in the Velphoro 1000 to 2000 mg/day dose groups (ranging from 35.0% to 42.9%). At the stage 2 baseline (Week 24) in Study PA-CL-05A, 72.7% of subjects in the MD group and 61.2% in the LD were within the KDOQI target range. At the end of stage 2 (Week 27) in this pivotal study, control of serum phosphorus was well maintained in the MD group, with 63.2% of subjects in the target range. In the LD group, withdrawal of the effective dose led to loss of control, with only 15.2% in the target range, similar to the LD group in PA-CL-03A after 6 weeks of treatment with 250 mg/day Velphoro.

The effect of Velphoro on the reduction of serum phosphorus levels was consistent across all subgroups and was not affected by other baseline or disease characteristics including region (Europe, US, and rest of the world), dialysis type (HD or PD), sex, age (<65 years or ≥65 years), race (Black, White or Other), ethnicity (Hispanic or Non-Hispanic), reason for ESRD (hypertension, diabetes or other), time from first dialysis, number of prior phosphate binders (1 or 2 or more), or prior sevelamer use (yes or no).

In conclusion, the efficacy of Velphoro for controlling serum phosphorus levels has been demonstrated. There is evidence of a dose-dependent relationship and treatment effects appear to be maintained at least 12 months based on the pivotal Study of PA-CL-05A and its extension study, 05B. A statistically significant difference in serum phosphorus levels between the maintenance dose and the low (non-effective) dose was observed as early as one week in the randomized withdrawal phase of the pivotal trial. Based on these findings, dose titration for controlling hyperphosphatemia can be started as early as 1 week after treatment initiation and adjusted at weekly intervals thereafter if necessary.

8. Safety

Safety data are mainly from 4 clinical studies conducted in ESRD patients undergoing dialysis including the pivotal efficacy study, its extension trial (Study PA-CL-05A/05B), one phase 2 dose-ranging study (Study PA-CL-03A) and one phase 2 study conducted in Japanese patients (Study PA1201). Clinical pharmacology studies, including one study, Study Q-24120, which was conducted in patients with chronic kidney disease, were also utilized in safety analyses.

Overall, 1953 subjects were included in the safety analysis including 1288 subjects who had received at least one dose of Velphoro. A total of 1355 ESRD patients were studied in short-term studies including 981 patients on Velphoro. A total of 659 ESRD patients were in an open-label, long-term study of up to 12 months including 391 ESRD patients on Velphoro.

Like other phosphate binders, drug-related AEs were primarily limited to GI effects. In the pivotal study, diarrhea was the most common Velphoro -related adverse event (AE) and was

also the major reason for AE-related patient withdrawal in the Velphoro group. The incidence rate of diarrhea was higher in the Velphoro group compared to the active control, sevelamer. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment. A dose-dependent increase in the incidence rate of diarrhea was found in Japanese patients in Study PA1201. However, in the fixed dose ranging study, Study PA-CL-03A, the incidence rate of diarrhea in this study was not related to dose and was similar in the Velphoro and sevelamer treatment arms.

Other common GI AEs including nausea, vomiting and constipation occurred less frequently on Velphoro than on sevelamer in the pivotal study. The incidence of common GI events was substantially reduced during continued treatment in the long-term extension study (Study PA-CL-05B). Hypophosphatemia was observed in some patients in both the dose-ranging study and the pivotal study. Given the drug's mechanism of action and intended effect, this is an expected dose-dependent drug-related AE. However, as this product will be started at a low dose and gradually titrated based on phosphate levels with careful monitoring, this AE does not represent a major safety concern. The treatment related AEs in the pivotal study and its extension are summarized in the following table. No new or significant safety signals emerged with long-term treatment of up to one year duration. In general, the incidence of Velphoro related AEs was similar to that observed with the active control, sevelamer.

Summary of treatment-related AEs in Study PA-CL-05A/05B

MedDRA SOC Preferred Term	PA-CL-05A/PA-CL-05B(1) (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any Treatment-related TEAE	320 (45.3%) 600	86 (24.7%) 152	57 (14.6%) 81	24 (9.0%) 30
Faeces discoloured	110 (15.6%) 112	1 (0.3%) 1	3 (0.8%) 3	0 (0.0%) 0
Diarrhoea	92 (13.0%) 131	8 (2.3%) 9	7 (1.8%) 10	0 (0.0%) 0
Hypophosphataemia	28 (4.0%) 38	13 (3.7%) 15	18 (4.6%) 22	7 (2.6%) 7
Hyperphosphataemia	24 (3.4%) 29	6 (1.7%) 6	8 (2.0%) 9	6 (2.2%) 7
Nausea	28 (4.0%) 30	18 (5.2%) 18	3 (0.8%) 3	0 (0.0%) 0
Product taste abnormal	27 (3.8%) 27	2 (0.6%) 2	4 (1.0%) 4	0 (0.0%) 0
Constipation	21 (3.0%) 23	17 (4.9%) 19	4 (1.0%) 4	2 (0.7%) 2
Vomiting	15 (2.1%) 16	4 (1.1%) 4	2 (0.5%) 2	0 (0.0%) 0
Dyspepsia	14 (2.0%) 17	6 (1.7%) 8	1 (0.3%) 1	2 (0.7%) 3
Abdominal pain	11 (1.6%) 12	4 (1.1%) 4	0 (0.0%) 0	0 (0.0%) 0
Tooth discolouration	10 (1.4%) 10	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Abdominal pain upper	8 (1.1%) 9	5 (1.4%) 5	1 (0.3%) 1	0 (0.0%) 0
Flatulence	7 (1.0%) 7	6 (1.7%) 7	0 (0.0%) 0	0 (0.0%) 0
Oral administration complication	7 (1.0%) 7	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Blood phosphorus increased	5 (0.7%) 5	4 (1.1%) 4	2 (0.5%) 2	4 (1.5%) 4
Decreased appetite	3 (0.4%) 3	4 (1.1%) 5	0 (0.0%) 0	0 (0.0%) 0

1 PA21 group includes subjects in PA-CL-05A Stage 2.

(Sponsor table from 120-day safety update report)

Summary of treatment-related AEs in Study PA-CL-03A

System Organ Class Preferred Term	PA21						Sevelamer (HCl) (N=26) n (%)
	1.25 g/Day (N=26) n (%)	5.0 g/Day (N=26) n (%)	7.5 g/Day (N=25) n (%)	10.0 g/Day (N=27) n (%)	12.5 g/Day (N=24) n (%)	Total PA21 (N=128) n (%)	
	# Events	# Events	# Events	# Events	# Events	# Events	# Events
Any TEAE	5 (19.2%)	9 (34.6%)	8 (32.0%)	12 (44.4%)	10 (41.7%)	44 (34.4%)	8 (30.8%)
	6	29	15	16	12	78	8
Gastrointestinal Disorders	2 (7.7%)	3 (11.5%)	6 (24.0%)	6 (22.2%)	4 (16.7%)	21 (16.4%)	4 (15.4%)
	2	21	10	8	5	46	4
Constipation	0 (0.0%)	1 (3.8%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	0 (0.0%)
	0	5	1	0	0	6	0
Diarrhoea	0 (0.0%)	1 (3.8%)	2 (8.0%)	1 (3.7%)	1 (4.2%)	5 (3.9%)	3 (11.5%)
	0	7	5	1	1	14	3
Faeces discoloured	2 (7.7%)	3 (11.5%)	3 (12.0%)	4 (14.8%)	3 (12.5%)	15 (11.7%)	0 (0.0%)
	2	3	3	4	3	15	0
Flatulence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
	0	0	0	0	1	1	0
Vomiting	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	2 (1.6%)	0 (0.0%)
	0	5	0	1	0	6	0
Metabolism and Nutrition Disorders	3 (11.5%)	4 (15.4%)	4 (16.0%)	7 (25.9%)	6 (25.0%)	24 (18.8%)	4 (15.4%)
	4	5	5	7	7	28	4
Hyperphosphataemia	3 (11.5%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.1%)	1 (3.8%)
	4	1	0	0	0	5	1
Hypophosphataemia	0 (0.0%)	3 (11.5%)	2 (8.0%)	7 (25.9%)	5 (20.8%)	17 (13.3%)	2 (7.7%)
	0	4	2	7	6	19	2

Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as Velphoro drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of Velphoro . (Sponsor table from the Study PA-CL-03A study report)

Because Velphoro is an iron based phosphate binder, the effect of Velphoro on systemic iron levels was evaluated in the pivotal study and its extension trial. Increases in serum ferritin and TSAT and decreases in transferrin were observed during the first 6 months of treatment with Velphoro compared to both baseline and the active control (20.3% vs. 5.1% from baseline for transferrin, 18.4% vs. -3.6% from baseline for TSAT, and -2.3% vs. 8.3% for transferrin, in the Velphoro vs. Sevelamer treatment arms, respectively). These effects were maintained but did not increase further with continued treatment up to one year as shown in the table below. There was no evidence of iron accumulation with increased cumulative exposure. Concomitant use of IV iron and ESAs in these studies and regional differences in use complicate the interpretation of these analyses. The observed changes, however, are consistent with the minimal iron absorption from Velphoro observed in the Phase 1 study and do not raise a major safety concern.

Summary of iron parameters in Studies PA-CL-05A/05B

Parameter / Time Point	(PA-CL-05A/PA-CL-05B) (SS)				(PA-CL-05A and PA-CL-05B) (Completers)			
	PA21 (N=707)		Sevelamer (N=348)		PA21 (N=322)		Sevelamer (N=227)	
	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Ferritin (ng/mL)								
Baseline [1]								
n	707	–	348	–	322		227	
Mean (SD)	666.6 (439.55)	–	714.5 (521.89)	–	621.5 (423.19)		710.1 (461.14)	
Median	603.9	–	630.9	–	574.8		680.0	
Min/max	9.8/3,043.2	–	9.3/4,742.8	–	9.8/2,115.7		9.3/2,186.0	
Week 24								
n	512	512	287	287	310	310	221	221
Mean (SD)	780.7 (492.80)	135.0*^ (340.33)	753.8 (494.81)	36.3^ (384.00)	722.0* (458.97)	116.7* (316.99)	763.1 (475.40)	51.0* (344.35)
Median	722.0	108.0	726.7	18.0	660.7	95.5	743.0	32.0
Min/max	8.9/2,975.5	-1,613.7/2,654.2	4.0/3,061.4	-3,320.0/1,690.0	8.9/2,061.9	-1,613.7/1,174.9	9.8/2,917.0	-1,234.0/1,690.0
Week 52								
n	321	321	229	229	319	319	227	227
Mean (SD)	776.7 (473.82)	152.4* (354.11)	776.7 (518.03)	70.9* (394.41)	776.1 (475.25)	152.7* (353.69)	781.6 (517.31)	71.5* (396.09)
Median	757.0	145.0	766.4	54.0	753.0	145.0	768.0	56.5
Min/max	15.6/2,468.0	-1,605.3/1,370.0	12.9/3,514.9	-1,302.0/2,397.9	15.6/2,468.0	1,605.3/1,370.0	12.9/3,514.9	-1,302.0/2,397.9
Iron (mcg/dL)								
Baseline [1]								
n	707	–	348	–	322	–	227	–
Mean (SD)	64.7 (31.12)	–	67.1 (29.06)	–	65.3 (25.61)	–	66.5 (25.61)	–
Median	58.0	–	63.0	–	59.9	–	62.0	–
Min/max	10.1/250.0	–	11.2/239.0	–	10.1/207.8	–	11.2/157.5	–
Week 24								
n	511	511	287	287	309	309	221	221
Mean (SD)	75.4 (32.15)	10.6* (36.96)	72.1 (35.25)	4.4 (38.54)	75.0 (30.62)	9.9* (34.85)	73.3 (34.12)	7.0* (34.97)
Median	69.0	11.0	64.8	2.0	69.0	10.6	66.0	3.4
Min/max	20.0/268.7	-162.6/235.2	17.3/217.0	-201.0/183.0	20.0/196.0	-162.6/128.0	17.3/217.0	-70.9/183.0
Week 52								
n	321	321	229	229	319	319	227	227
Mean (SD)	73.1 (33.66)	7.8* (39.46)	73.7 (33.59)	7.1* (32.75)	73.1 (33.68)	7.7* (39.50)	73.6 (33.71)	7.1* (32.88)
Median	65.4	7.0	67.0	3.0	65.4	7.00	66.5	3.0
Min/max	17.3/217.0	-116.0/177.0	21.0/198.0	-71.5/149.0	17.3/217.0	-116.0/177.0	21/198.0	-71.5/149.0

Summary of iron parameters in Studies PA-CL-05A/05B (con't)

Parameter / Time Point	(PA-CL-05A/PA-CL-05B) (ITT)				(PA-CL-05A and PA-CL-05B) (Completers)			
	PA21 (N=707)		Sevelamer (N=348)		PA21 (N=322)		Sevelamer (N=227)	
	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Transferrin (mcg/dL)								
Baseline [1]								
n	707	–	348	–	322	–	227	–
Mean (SD)	2,288.8 (481.69)	–	2,274.9 (456.59)	–	2,314.5 (482.83)	–	2,291.4 (462.16)	–
Median	2,218.8	–	2,238.2	–	2,296.2	–	2,244.6	–
Min/max	967.5/5,200.0	–	1,290.0/4,500.0	–	967.5/5,200.0	–	1,290.0/4,500.0	–
Week 24								
n	510	510	287	287	308	308	221	221
Mean (SD)	2,238.7 (432.61)	-53.6*^ (295.74)	2,472.9 (496.76)	189.3*^ (311.06)	2,248.1 (428.31)	-63.7*^ (306.46)	2,463.8 (481.41)	176.6*^ (310.89)
Median	2,186.6	-51.6	2,400.0	200.0	2,218.8	-77.4	2,400.0	200.0
Min/max	967.5/4,300.0	-1,200.0/800.0	1,431.9/4,300.0	-1,900.0/1,400.0	967.5/4,300.0	-1,200.0/800.0	1,431.9/4,300.0	-1,900/1,400.0
Week 52								
n	321	321	229	229	319	319	227	227
Mean (SD)	2,196.5 (404.54)	-121.6*^ (324.47)	2,450.3 (460.63)	150.9*^ (341.76)	2,192.7 (402.90)	-121.3*^ (325.44)	2,445.4 (457.33)	154.0*^ (341.15)
Median	2,100.0	-100.0	2,400.0	154.8	2,100.0	-100.0	2,400.0	154.8
Min/max	967.5/4,000.0	-1,600.0/900.0	1,600.0/3,900.0	-1,800.0/1,032.0	967.5/4,000.0	-1,600.0/900.0	1,600.0/3,900.0	-1,800.0/1,032.0
Transferrin Saturation (%)								
Baseline [1]								
n	706	–	348	–	321		227	
Mean (SD)	26.6 (13.70)	–	27.8 (13.78)	–	26.5 (13.28)		27.4 (12.25)	
Median	24.0	–	25.5	–	24.0		25.0	
Min/max	2.0/95.0	–	3.0/117.0	–	2.0/95.0		3.0/90.0	
Week 24								
n	509	509	287	287	307	307	221	221
Mean (SD)	31.4 (14.09)	4.9*^ (16.12)	27.5 (15.29)	-0.6*^ (17.30)	31.2 (13.91)	4.6*^ (15.76)	28.1 (15.06)	0.7^ (15.24)
Median	29.0	5.0	24.0	-1.0	29.0	5.0	25.0	-1.0
Min/max	7.0/101.0	-66.0/72.0	4.0/101.0	-98.0/74.0	7.0/101.0	-66../71.0	4.0/101.0	-44.0/74.0
Week 52								
n	320	320	229	229	318	318	227	227
Mean (SD)	31.0 (15.17)	4.6* (17.93)	28.4 (14.97)	1.0 (14.72)	31.0 (15.19)	4.5* (17.97)	28.4 15.02)	1.0 (14.78)
Median	28.0	4.0	26.0	-1.0	28.0	4.0	26.6	-1.0
Min/max	6.0/95.0	-60.0/78.0	7.0/109.0	-38.0/87.0	6.0/95.0	-60.0/78.0	7.0/109.0	-38.0/87.0

Baseline was defined as the last non-missing value prior to or on the date of the first PA-CL-05A study drug intake.

In conclusion, the size of the safety database and duration of exposure are adequate to assess safety for this product. Overall, the AE profile of Velphoro is acceptable for the control of serum phosphorus levels in patients with end stage renal disease who are being treated with chronic hemodialysis or peritoneal dialysis.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Treatment effects on serum phosphorus levels have been used to establish the efficacy of other phosphate binders and there were no significant safety issues that required discussion.

10. Pediatrics

PREA requirements were discussed with the applicant at a meeting on August 13, 2010. At the meeting, the Division and the Office of Pediatrics and Maternal Health Staff (PMHS) agreed with the applicant that pediatric studies could be deferred until adult studies were completed (b) (4) The applicant would not request a waiver.

(b) (4) The NDA review team and the reviewers from PMHS felt that the overall study design was reasonable, though some modifications should be made. The sponsor agreed to implement the Agency's advice. The PeRC PREA Subcommittee considered the overall study plan to be acceptable. A detailed study protocol has not yet been submitted.

11. Other Relevant Regulatory Issues

Financial disclosures: Financial disclosures have been adequately addressed (see Section 3.3 of the Clinical Review)

Clinical inspection: Three US sites were chosen because of high enrollment rates and a larger number of responders. According to the report from the Office of Science Investigation (OSI), these sites conducted the studies adequately. OSI did not identify any disqualifying problems at these sites and concluded that the data from these sites were acceptable.

12. Labeling

The proposed proprietary name Velphoro (b) (4) has been reviewed by the Division of Medication Error Prevention and Analysis and is found acceptable from both a promotional and safety perspective. The previous proposed proprietary name, (b) (4) was found unacceptable (b) (4)

A draft labeling containing the Division's recommendations has been shared with the Applicant. As noted in sections 7 and 13, revisions are needed to the text describing drug-drug interactions and non-clinical toxicology findings; some other changes in wording and corrections have also been made. Agreement needs to be reached prior to approval.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action:

Pending agreement on labeling, I recommend that Velphoro (PA21) be approved for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on hemodialysis (HD) or peritoneal dialysis (PD) therapy.

- Risk Benefit Assessment

The efficacy of Velphoro for the control of serum phosphorus level in ESRD patients on dialysis was demonstrated in a pivotal study and a dose-ranging study. The development program also provides evidence of the product's long-term effectiveness in controlling serum phosphorus levels.

As with other non-absorbed medicines, safety findings were primarily limited to GI adverse events. Diarrhea was the most common adverse event on Velphoro. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued use of Velphoro. No new or significant safety signals have emerged with long-term treatment in the safety extension study, and the findings from this study suggest maintenance of efficacy with chronic administration and a favorable tolerability profile. No safety concerns were raised by a comprehensive assessment of laboratory tests which included hematology and chemistry tests and ECGs. No significant iron accumulation was observed during treatment for up to 52 weeks in a long term study. The effects of Velphoro™ on the bioavailability of other drugs commonly used in ESRD patients have also been sufficiently characterized for the purpose of labeling.

Overall, Velphoro has a favorable benefit/risk profile as a treatment for the control of serum phosphorus levels in patients with ESRD.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Based on the information available in the current submission, I do not have any recommendations for post market risk evaluation and mitigation strategies.

- Recommendation for other Postmarketing Requirements and Commitments

Pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) should be conducted but will be deferred until after approval. The applicant has submitted their pediatric plan [redacted] (b) (4)

- Recommended Comments to Applicant

See comments under "Labeling". Agreement needs to be reached prior to approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEN XIAO
11/08/2013

ALIZA M THOMPSON
11/08/2013