DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 25, 2024

APPLICATION/DRUG: NDA 205109s009/Velphoro (ferric oxyhydroxide)

APPLICANT: Fresenius Medical Care North America

SUBJECT: Data to Support Dosing of Pediatric Patients Down to 9 Years of Age for the Proposed Indication

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Background and Relevant Regulatory History

Velphoro (ferric oxyhydroxide, PA21) is an iron-based phosphate binder that is approved as a 500 mg chewable tablet for the control of serum phosphorus levels in adults with chronic kidney disease (CKD) on dialysis. At the time of approval on November 27, 2013, the Agency issued a post-marketing requirement (PMR) for a deferred efficacy and safety study under the Pediatric Research Equity Act for pediatric patients 1 month to 17 years of age with advanced CKD; the PMR was subsequently changed to a safety, tolerability, and pharmacodynamic study in patients 2 to 17 years of age. The Agency also issued a Written Request (WR) for the pediatric study.

To address the PREA requirements and terms of the WR, the Applicant conducted an open-label, randomized, active-controlled, multicenter study in pediatric patients birth to 17 years of age with hyperphosphatemia and stage 4 or 5 CKD (estimated glomerular filtration rate <30 mL/min/1.73 m^2) or stage 5D CKD receiving maintenance hemodialysis or peritoneal dialysis (Study PA-CL-PED-01). (b) (4)
(b) (4)

On July 7, 2021, the Agency issued Complete Response letters under NDA 205109s009 (b) (4)

[1] Multi-disciplinary Collaborative Review dated July 7, 2024 (DARRTS Reference ID: 4822587)
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(b) (4) because of a lack of agreement on the identification of the active ingredient. The Agency also indicated that the application lacked sufficient data (b) (4) in pediatric patients 2 to <6 years of age (b) (4) (b) (4) To address the latter issue, the Division recommended obtaining additional data in patients 2 to <6 years of age (b) (4)

Of note, after discussion with the Pediatric Review Committee (PeRC), the Agency considered the PREA PMR fulfilled. The Applicant also received pediatric exclusivity because they met the terms of the WR.

(b) (4)

In the current submission, the Applicant responded to the Agency's July 7, 2021, Complete Response letter and proposes to expand the indicated population to pediatric patients (b) (4) (b) (4) using the currently approved 500 mg chewable tablet based on data from Study PA-CL-PED-01 submitted on July 7, 2021, and previously reviewed by the Agency.[1] The Applicant did not submit additional clinical data with the current Complete Response.

Data to Support Dosing Down to 9 Years of Age Using the 500 mg Chewable Tablet
During its review of the Applicant's Complete Response, the Agency questioned whether the currently approved 500 mg chewable tablet could support dosing and titration of Velphoro for pediatric patients down to 9 years of age with hyperphosphatemia (as opposed to the Applicant's proposal (b) (4)). To address this issue, additional analyses of the data from Study PA-CL-PED-01 were conducted.

The study consisted of a screening period of up to 4 weeks, a washout period of up to 3 weeks for patients previously taking phosphate binders, a dose titration period of up to 10 weeks (Stage 1), and a 24-week safety extension (Stage 2). Patients were followed up 14 days after their last Stage 2 study visit. As noted in the Agency's 2021 review, patients 9 to 18 years of age were dosed using the 250 mg or 500 mg powder for oral suspension or the 250 mg or 500 mg chewable tablets.[1]

Based on review of the results of Study PA-CL-PED-01 during the original 2021 review cycle for the 500 mg chewable tablet (b) (4) the Agency determined that dosing was supported down to 6 years of age. The table below shows the starting and dose titration steps for Velphoro by age group for pediatric patients with hyperphosphatemia that were supported by the data.

Recommended Velphoro Starting Doses and Dose Titrations for Pediatric Patients

Age (Years)	Daily Starting Dose	Dose Increases or Decreases	Maximum Recommended Daily Dose
6 to <9	750 mg	125, 250 or 375 mg	2,500 mg
9 to <12	1,000 mg	250 or 500 mg	3,000 mg
12 to <18	1,500 mg	500 mg	3,000 mg

As shown in the table below, the Velphoro dosing regimen evaluated in the study reduced mean serum phosphorus levels in patients 9 to <12 years of age during Stage 1 and the effect persisted through Stage 2.

Change from Baseline in Serum Phosphorus Levels in the Velphoro Arm in Study PA-CL-PED-01

Age (years)	n	Change from Baseline in Serum Phosphorus (mg/dL) to End of Stage 1 (mean±SD)
9 to <12	10	-1.37±1.39
12 to 18	46	-0.57±1.45

Age (years)	n	Change from Baseline in Serum Phosphorus (mg/dL) to End of Stage 2 (mean±SD)
9 to <12	5	-1.19±2.37
12 to 18	27	-0.59±1.88

Analyses conducted by Clinical Pharmacology reviewer

Information on the maximum and median daily dose of Velphoro received is shown in the table below.

Velphoro Dosing Information Based on Age

Stage	Age (years)	Maximum daily dose (mg Iron/day) Median (min, max)	Average daily dose (mg Iron/day) Median (min, max)
1	9 to <12 (n=10)	1500 (1250, 2750)	1216 (733, 1623)
	12 to 18 (n=45)	1750 (500, 3000)	1338 (308, 2688)
2	9 to <12 (n=7)	1750 (750, 3000)	1633 (750, 3000)
	12 to 18 (n=29)	2000 (220, 3969)	1258 (308, 2688)

Analyses conducted by Clinical Pharmacology reviewer

Conclusion

Age Range

In summary, the results from Study PA-CL-PED-01 support dosing and titration of Velphoro for pediatric patients 9 to <18 years of age using the 500 mg chewable tablet. For patients 9 to <12 years of age, the starting dose of 1,000 mg daily as well as the maximum dose of 3,000 mg is supported by the 500 mg strength chewable tablet. Although the study allowed dose titrations of 250 mg or 500 mg in patients 9 to <12 years of age, the Division believes that dose titrations at the higher 500 mg level would be acceptable because prescribers could monitor for adverse reactions (e.g., gastrointestinal effects, hypophosphatemia) and decrease the Velphoro dose as

needed. Hence, the Agency supports approval of the 500 mg dosage strength for pediatric patients 9 years of age and older.

Prescribing Information
The Division of Pediatric and Maternal Health (DPMH) was involved in labeling discussions. Section 8.4 Pediatric Use will include statements indicating that

- Velphoro is indicated for the control of serum phosphorus levels in pediatric patients 9 years of age and older with CKD on dialysis
- Although the safety and effectiveness have been established for patients 6 to <9 years of age with hyperphosphatemia, the product is not approved in this age group because of the lack of an appropriate dosage strength
- The safety and effectiveness of Velphoro have not been established in pediatric patients younger than 6 years of age. Although the study included six patients 2 to <6 years of age, who received Velphoro, based on the available data, it is unclear whether the dosing regimen that was evaluated is effective in reducing serum phosphorus in this age group
- Velphoro has not been studied in pediatric patients below 2 years of age

Section 14.3 Pediatric Study will include a description of the study for patients 6 to 18 years of age, i.e., the population for whom data from the pediatric study support dosing of Velphoro; however, dosing information will only be provided for patients 9 years of age and older (the approved/indicated population) to avoid giving the impression that the current 500 mg chewable tablet is approved for patients <9 years of age.

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/s/

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