Cross-Discipline Team Leader and Division Summary Review

Date	July 1, 2024
From	Aliza Thompson, M.D., M.S. Deputy Director, Division of Cardiology and Nephrology
Application Number/Type	NDA 205109/S-009; Class 2 resubmission
Applicant	Vifor Fresenius Medical Care Renal Pharma France
Date of Receipt	January 5, 2024
PDUFA Goal Date	July 5, 2024
Established name/Proprietary name	Sucroferric oxyhydroxide/Velphoro
Dosage Form/Strength	Chewable tablet/ 500 mg
Proposed Indication	Expansion of current indication in adults to include pediatric patients (b)(4) years of age and older with chronic kidney disease on dialysis
Regulatory Action	Approval
Approved Indication	Expansion of current indication in adults to include pediatric patients 9 years of age and older with chronic kidney disease on dialysis

This review is based on the reviews and memos listed below:

Material Reviewed/Consulted	**Review Team**
Office of Pharmaceutical Quality Review (June 26, 2024)	Parvin Akther, Gurpreet Gill Sangha
Clinical and Clinical Pharmacology Memo (June 25, 2024)	Kirtida Mistry, Li Wang, Brianna Cote, Aliza Thompson
Office of Prescription Drug Promotion Labeling Review (June 11, 2024)	Charuni Shah, Sapna Shah
Office of Surveillance and Epidemiology – Division of Medication Error Prevention and Analysis Labeling Review (June 5, 2024)	Sue Black, Nicole Iverson

1. Background

Velphoro (sucroferric oxyhydroxide) is an iron-based phosphate binder that is approved as a chewable tablet for the control of serum phosphorus levels in adults with chronic kidney disease (CKD) on dialysis. Hyperphosphatemia is common in patients with kidney failure treated with dialysis and has been associated with secondary hyperparathyroidism, vascular, valvular,

and other soft tissue calcification, cardiovascular disease, and death. In pediatric patients with CKD, hyperphosphatemia and secondary hyperparathyroidism is also associated with poor growth, skeletal maturation delay, and skeletal deformities. Although several agents are approved to control serum phosphorus levels in adults with CKD on dialysis, only one (sevelamer carbonate) is approved for use in pediatric patients (down to 6 years of age).

On January 7, 2021, Vifor Fresenius Medical Care Renal Pharma France submitted (b) (4) (b) (4) a labeling supplement to NDA 205109 (NDA for the chewable tablet dosage form) for the following additional indication (b) (4) This submission was intended to fulfil a Pediatric Research and Equity Act (PREA) post-marketing requirement (PMR) and a Written Request. In support of the proposed indication, the Applicant submitted the results of Study PA-CL-PED-01, an open-label, randomized, active-controlled, multicenter study conducted in pediatric patients 2 to 17 years of age with hyperphosphatemia and advanced CKD (defined as an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or CKD on dialysis). Given its mechanism of action, Velphoro, if administered at an appropriate dose, is expected to be effective in lowering serum phosphorus levels. As such, the goal of the study, from an FDA perspective, was to obtain information to support dosing and to assess safety and tolerability.

On June 7, 2021, the Agency issued a general advice letter indicating that pediatric exclusivity was granted. On July 7, 2021, the Agency issued Complete Response (CR) letters (b) (4) (b) (4) related to disagreement on the identification of the active ingredient (the Agency had determined that the active ingredient is ferric oxyhydroxide and not sucroferric oxyhydroxide) and insufficient data (b) (4) in pediatric patients 2 to <6 years of age. To address the latter issue, the Agency recommended obtaining additional data in patients 2 to <6 years of age (b) (4) On February 17, 2022, the Agency issue a letter indicating the PMR was fulfilled.

The current submission contains the Applicant's complete response to the deficiencies cited in the Agency's CR letter. The submission includes the Applicant's justification for retaining sucroferric oxyhydroxide as the active ingredient and established name of Velphoro. In response to the Agency's concern about the data provided (b) (4) in pediatric patients 2 to < 6 years of age, the Applicant proposes to expand the current indication for Velphoro in adults to pediatric patients (b) (4) using the currently approved 500 mg chewable tablet.[1]

(b) (4)

2. Product Quality and Active Ingredient/Established Name

The Office of Pharmaceutical Quality (OPQ) recommends approval of this NDA from a quality perspective. As discussed in the OPQ review, on May 26, 2021, FDA issued its response to citizen petition Docket No. FDA-2016-P-1163, which was submitted by Foley & Hoag LLP on behalf of Vifor Fresenius Medical Care Renal Pharma France on April 15, 2016 (Vifor). In that response, FDA noted that the active moiety of multiple iron products is ferric oxyhydroxide and that, as a result, the product at issue was not eligible for new chemical entity exclusivity. Although the active ingredient identity for those products was not directly at issue in that citizen petition, FDA also noted its conclusion that the active ingredient was ferric oxyhydroxide, thus addressing an argument by the petitioner that the active ingredient, and not the active moiety was the relevant entity for determining new chemical entity exclusivity. FDA also indicated its intention to take additional steps to ensure the non-proprietary names for certain iron-containing products reflected this active ingredient determination.

On August 3, 2021, Vifor submitted a new citizen petition, which was docketed as FDA-2021-P-0893. This new petition asks that FDA reconsider its findings in the Agency's citizen petition response to the April 15, 2016 citizen petition in Docket No. FDA-2016-1163. Of note, following Vifor's submission of its April 15, 2016 citizen petition, but before FDA's response on May 26, 2021, the relevant statutory provisions in the Federal Food, Drug, and Cosmetic Act (FD&C Act) regarding new chemical entity exclusivity were amended by the Ensuring Innovation Act (Pub. L. No. 117-9 (Apr. 23, 2021)) making explicit in the FD&C Act that active moiety, and not active ingredient, is the relevant inquiry for new chemical entity exclusivity determinations. In addition, despite the passage of time, no sponsor of a marketed iron product subject to the May 26, 2021 citizen petition response has updated its labeling to identify ferric oxyhydroxide as the active ingredient.

In light of the foregoing, and as a result of Vifor's submission of its August 3, 2021 Citizen Petition, the Center for Drug Evaluation and Research (CDER) is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021 Citizen Petition response is ferric oxyhydroxide. While CDER's reevaluation is ongoing, CDER is accepting the iron complex as the active ingredient name for all iron products subject to the May 26, 2021 Citizen Petition response. As such, the deficiency requesting that the applicant revise the proposed labeling to indicate that the active ingredient and established name of Velphoro is ferric oxyhydroxide is resolved. The active ingredient and established name of the product will continue to be identified in labeling as sucroferric oxyhydroxide at this time.

3. Clinical

During the prior review cycle for the 500 mg chewable tablet (b) (4) In its CR Letter, the Agency indicated that the application lacked sufficient data (b) (4) in pediatric patients 2 to <6 years of age and encouraged the Applicant to obtain additional data to support dosing in this age group. In the current

submission, the Applicant proposes to expand the indicated population for Velphoro 500 mg chewable tablets to pediatric patients [redacted](b) (4)

The review team conducted further analyses of Study PA-CL-PED-01 to determine whether the currently approved 500-mg chewable tablet could support dosing and titration of Velphoro for pediatric patients down to 9 years of age [redacted](b) (4) [redacted](b) (4) As discussed in the joint clinical and clinical pharmacology memo, although Study PA-CL-PED-01 allowed dose titrations of 250 mg or 500 mg in patients 9 to <12 years of age, dose titrations at the higher 500-mg level would be acceptable in this age group because prescribers could monitor for adverse reactions (e.g., gastrointestinal effects, hypophosphatemia) and decrease the Velphoro dose as needed. Hence, the 500-mg dosage strength can be approved for use in pediatric patients down to 9 years of age.

4. Labeling

The Division of Pediatric and Maternal Health was involved in labeling discussions. For an overview of key labeling considerations, see the joint clinical and clinical pharmacology memo. The Agency's labeling recommendations were communicated to the Applicant and the labeling has been revised to address the Agency's feedback. There are no outstanding labeling issues at this time.

5. Recommended Regulatory Action

Approval for the control of serum phosphorus levels in adults and pediatric patients 9 years of age and older with CKD on dialysis

6. Postmarketing Requirements and Commitments

None.

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/s/

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