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January 11, 2023

Division of Dockets Management,
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

SUPPLEMENT TO CITIZEN PETITION

Re: Docket No. FDA-2022-P-0144

To Whom It May Concern:

The undersigned submits this citizen petition supplement, pursuant to 21 C.F.R. § 10.30(g), to update the administrative record with information from certain recent publications that relate to the requests set forth in the February 3, 2022 citizen petition relating to Injectafer® (ferric carboxymaltose injection). Specifically, the original petition requested that the Food and Drug Administration ("FDA") deny any Injectafer sNDAs for labeling changes based on deficient clinical trials, strengthen Injectafer warnings and precautions with regards to severe hypophosphatemia and its consequences, and require any future indications to be based on clinical trials that specifically assess the risk of hypophosphatemia.[1] The recent publications submitted with this supplement both support and complement the arguments of the original citizen petition, adding further support and urgency to the requests.

As discussed more fully below, the recent publications highlight the product-specific concerns relating to the use of Injectafer in heart failure patients, including its unique tendency to cause severe hypophosphatemia and cardiac hypertrophy due to its impact in driving dramatic increases in the active form of fibroblast growth factor 23 ("FGF23"). Moreover, the recent publications confirm that Injectafer, unlike at least one other intravenous iron replacement product (ferric derisomaltose), has not shown an apparent benefit in heart failure patients with nonischemic disease. Accordingly, as requested in the February 2022 petition, FDA should require any new indications for Injectafer to be based on well-controlled clinical studies that specifically assess the risks of severe and symptomatic hypophosphatemia and should require further information from long-term clinical studies to do a risk-benefit analysis on Injectafer, especially before granting any new indications directed to heart failure patients.

A. Actions Requested

As requested in the February 3, 2022 petition, the undersigned respectfully requests that FDA:

[1] February 3, 2022 Citizen Petition, Docket ID FDA-2022-P-0144-0001 at 1 (posted Feb. 9, 2022) (hereinafter, "Feb. 2022 Petition").

1. Deny any Injectafer sNDAs for any labeling changes based on the FAIR–HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless to add or strengthen a contraindication, warning, precaution, or adverse reaction.

2. Strengthen Injectafer warnings and precautions and its dosage and administration in relation to severe and symptomatic hypophosphatemia and its consequences.

3. Require any potential future expanded or additional indication for Injectafer to be based on well-controlled clinical studies that specifically assess the risks of severe and symptomatic hypophosphatemia and its consequences for such intended use.

B. A recent publication further highlights the risk of FGF23-derived safety concerns on hypophosphatemia following administration of Injectafer.[2]

A November 2022 publication from renowned cardiologist Dr. Milton Packer examines the available data for Injectafer, including the AFFIRM-AHF trial, which was discussed at length in the February 2022 petition. The Packer publication raises fundamental, product-specific concerns about the risk-benefit of Injectafer in heart failure patients: first, the apparent lack of benefit in heart failure patients with nonischemic etiology; and second, the product-specific tendency of Injectafer to drive dramatic increases in FGF23, leading to a risk of severe hypophosphatemia and potential risk of pathophysiological effects on the heart, including a tendency to cause hypertrophy.[3] In doing so, Dr. Packer asserts, consistent with the February 2022 petition, that the potential benefit of iron repletion on cardiovascular mortality may be counter-balanced by idiosyncratic features of Injectafer.[4]

As described by Dr. Packer, FGF23 downregulates the expression of sodium-phosphate cotransporters in the proximal tubule of the kidney and decreases the circulating concentration of 1,25-dihydroxyvitamin D.[5] An increase in FGF23 levels thus leads to severe hypophosphatemia in patients with heart failure.[6] In a single-center retrospective study measuring phosphate levels in 173 patients who received Injectafer, 47 (27%) experienced hypophosphatemia, with 44 (25%) classified as severe and 3 (2%) as extreme.[7] As discussed by Dr. Packer, the hypophosphatemia is also worsened if the patient receives repeated doses of Injectafer in an ongoing treatment, causing myopathy, osteomalacia, and fractures.[8] "Increases in FGF23 and associated hypophosphatemia typically last about 6 weeks, but FGF23 elevations and phosphate depletion can be profound when FCM (ferric carboxymaltose) [i.e., Injectafer] is given as an ongoing treatment."[9] Further, Dr. Packer notes that the increase in FGF23 levels

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[2] Milton Packer, *Increases in fibroblast growth factor 23 during treatment with ferric carboxymaltose: Potential adverse effects on the heart and kidneys*, J. CARDIAC FAILURE, Nov. 2022 at 1 (hereinafter, "Packer 2022") (attached as Exhibit A).
[3] *Id.*
[4] Feb. 2022 Petition at 14-16 ("The potential benefit of IV iron on cardiovascular mortality is counter-balanced by other properties caused by the Injectafer formulation – *e.g.*, the increase in FGF23.").
[5] *See* Packer 2022 at 1.
[6] *See id.*
[7] Alexander Dashwood, *Hypophosphatemia Is Common After Intravenous Ferric Carboxymaltose Infusion Among Patients With Symptomatic Heart Failure With Reduced Ejection Fraction*, 61 J. CLINICAL PHARMACOLOGY 515, 516 (2021) (attached as Exhibit B).
[8] *See* Packer 2022 at 1.
[9] *Id.* at 2.

causing phosphate depletion is observed with Injectafer, but not with other intravenous iron formulations, such as ferric derisomaltose.[10]

In addition to affecting kidney function, Dr. Packer recognizes that FGF23 has effects on heart function as well.[11] Increased levels of FGF23 precede and are an independent predictor of cardiac hypertrophy in patients with chronic kidney disease.[12] In fact, FGF23 is known to be the cause of cardiac hypertrophy because constitutive activation of FGF23 causes hypertrophy, and hypertrophy does not develop if the FGF23 receptor is suppressed.[13] Dr. Packer notes that increased FGF23 levels in patients with chronic kidney disease who are also iron-deficient mediates those patients' increased risk of heart failure. Furthermore, increased FGF23 has adverse prognostic significance in patients with established heart failure.[14] Patients with nonischemic cardiomyopathy and marked increases in FGF23 have the most striking declines in heart function.[15]

Thus, Dr. Packer's latest publication from November 2022 echoes the concerns that were raised in the February 2022 petition and highlights the further risk of FGF23-derived side effects following the administration of Injectafer. As explained more fully in the original petition, there is a need for more rigorous and long-term studies that specifically assess the benefits and risks of Injectafer in patients with heart failure and iron deficiency. The existing trials on Injectafer suffer from serious limitations that make it difficult to evaluate Injectafer's safety in the heart failure population, particularly given the risk of severe and symptomatic hypophosphatemia that has been repeatedly observed.[16] Because current Injectafer labeling does not adequately address these risks, FDA should revise the warning information to more clearly state the risk of FGF23-derived side effects and require future expanded or additional indications of Injectafer to be based on studies specifically assessing the risks of FGF23-derived side effects, including severe and symptomatic hypophosphatemia.

C. Results in other recent clinical trials suggest that alternative forms of iron repletion treatment may be more beneficial to patients, and demonstrate the need for further studies on Injectafer, especially in specific patient subgroups.

As discussed more fully in the February 2022 petition, the mediation of strong increases in the active form of FGF23 and the resulting dramatic increase in the risk of severe and symptomatic hypophosphatemia is a feature that is unique to Injectafer among the IV iron products available in the United States. In fact, in contrast to the AFFIRM-AHF study's findings on Injectafer that were discussed in the original petition,[17] a recent study published in November 2022 demonstrates that at least one other intravenous iron repletion product (ferric derisomaltose) does not present the same risks, highlighting the need for further studies and warnings for Injectafer.

Specifically, the IRONMAN trial published in November 2022 was the first large, randomized trial to investigate safety and long-term (multi-year) effects of intravenous iron in patients with heart failure. The trial made use of a different intravenous iron, ferric derisomaltose. The trial consisted of

[10] *See id.* at 1.
[11] *See id.*
[12] *See id.*
[13] *See id.* at 1-2.
[14] *See id.* at 2.
[15] *See id.*
[16] *Id.* at 16. For example, the AFFIRM-AHF trial's length of 52 weeks is insufficient in a fragile population like patients with heart failure, for whom long-term safety and efficacy data are essential.
[17] Feb. 2022 Petition at 16-17.

1,137 UK patients, aged 18 or older, with heart failure and iron deficiency, half of whom were assigned to receive ferric derisomaltose on top of usual care, with the other half receiving usual care alone. It was a prospective, randomized, open-label, blinded-endpoint trial done at 70 hospitals in the UK between August 25, 2016 to October 15, 2021, with a median follow-up of 2.7 years. The primary endpoint of the IRONMAN study was recurrent heart failure hospitalizations or cardiovascular death.[18] The study found that fewer patients experienced a primary endpoint if they had been randomized to receive ferric derisomaltose on top of usual care as compared to usual care alone.[19]

As discussed in the February 2022 petition, there was a lack of a numerical benefit on cardiovascular death for the administration of Injectafer in the AFFIRM-AHF trial.[20] In contrast, the IRONMAN trial showed a separation of the Kaplan-Meier curves for cardiovascular death (around a 14% relative risk reduction) in patients who received ferric derisomaltose compared to patients who did not receive any iron therapy.[21] The difference between the two trials can be visualized by comparing Figure 2D from the AFFIRM-AHF trial and Figure 2C in the IRONMAN trial publications, respectively.[22]

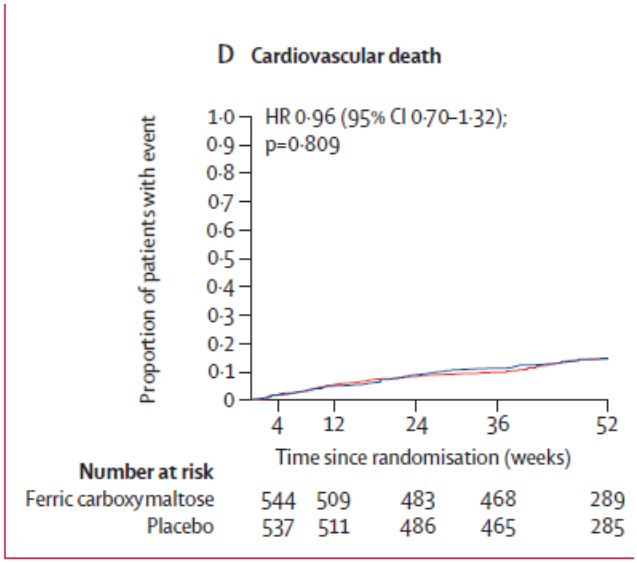

Fig. 2D, Kaplan-Meier curve of cardiovascular death outcomes from AFFIRM-AHF trial.
(HR = hazard ratio)

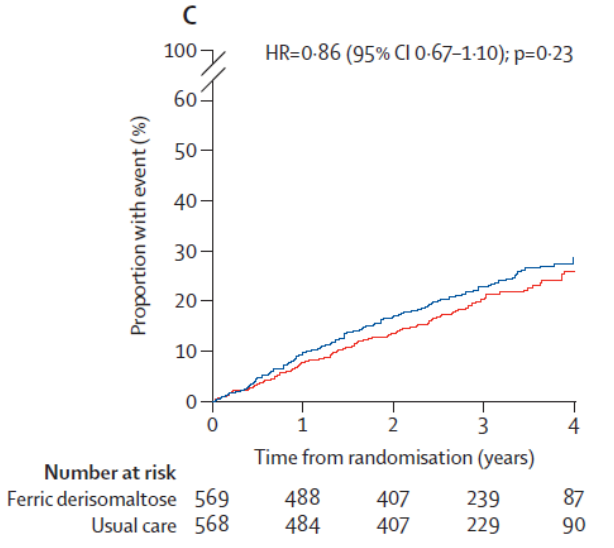

Fig. 2C, Kaplan-Meier curve of cardiovascular death outcomes from IRONMAN trial.
(HR = hazard ratio)

[18] Paul R. Kalra et al., *Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomized, open-label, blinded-endpoint trial*, LANCET, Nov. 2022 at 3 (hereinafter, "Kalra 2022") (attached as Exhibit C).
[19] Kalra 2022 at 1, 7.
[20] Feb. 2022 Petition at 16.
[21] *See* Kalra 2022 at 7.
[22] *Compare* Piotr Ponikowski et al., *Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial*, 398 LANCET 1895, 1899, Fig. 2D (2020) (attached as Exhibit D), *with* Kalra 2022 at 7, Fig. 2C.

Additionally, in the IRONMAN trial, patients in the ferric derisomaltose group obtained a homogenous risk reduction across subgroups. Specifically, unlike with Injectafer in the AFFIRM-AHF trial, the IRONMAN trial found that both subgroups containing patients with ischemic and non-ischemic etiology of heart failure benefitted from receiving ferric derisomaltose treatment with no significant interaction between the subgroups.[23]

As requested in the February 2022 petition, to help mitigate the potential of significant patient harm, FDA should thus require further information from long-term clinical studies to do a risk-benefit analysis on Injectafer, especially before granting any new indications directed to heart failure patients.

The results of the recently-published IRONMAN trial further support the actions requested. Given that the IRONMAN trial demonstrated that at least one other intravenous iron replacement product (ferric derisomaltose) benefits heart failure patients with both ischemic and non-ischemic etiology and given that it has been repeatedly recognized – including in Dr. Packer's recent November 2022 publication – that Injectafer uniquely presents risks of FGF23-derived side effects, including severe and symptomatic hypophosphatemia, FDA should require any new indications for Injectafer to be based on well-controlled clinical studies that specifically assess the hypophosphatemia risks and fully assess the risk-benefit of Injectafer administration across patient subgroups.

D. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this supplement to the petition includes all information and views on which it relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Sincerely,

Chad A. Landmon

[23] *See* Supplementary Appendix to Kalra 2022, LANCET, Nov. 2022 at 12, Figure S6A (relevant excerpt of appendix attached as Exhibit E).