Chad A. Landmon
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Hartford, CT 06103

May 31, 2023

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

Dear Mr. Landmon:

This letter responds to your citizen petition received February 8, 2022 (Petition). In the Petition, you request that the Food and Drug Administration (FDA, the Agency, or we):

1. Deny any Injectafer sNDAs [supplemental new drug applications] for any labeling changes based on the FAIR-HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended 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.

(Petition at 2).

We have carefully considered the Petition. For the reasons described below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Injectafer

Injectafer (ferric carboxymaltose injection) is an iron replacement product indicated for the treatment of iron deficiency anemia in adults and pediatric patients 1 year of age and older who have either intolerance or an unsatisfactory response to oral iron, and adult patients who have non-dialysis dependent chronic kidney disease, and iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity.[1]

Injectafer was approved on July 25, 2013, under new drug application (NDA) 203565, currently held by American Regent, Inc. The initial prescribing information included information on hypophosphatemia (described as a decrease in blood phosphorous) and hypophosphatemic

[1] Injectafer Prescribing Information (May 2023), at 1.

osteomalacia.[2] An sNDA approved February 19, 2020, included additional information on hypophosphatemia, including instructions to "[m]onitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment."[3]

Injectafer is distributed in 100 milligrams (mg) iron/2 milliliters (mL) single-dose vials, 750 mg iron/15 mL single-dose vials, and 1,000 mg iron/20 mL single-dose vials. For patients weighing 50 kilograms (kg) or more, the recommended dosage is 750 mg intravenously in two doses separated by at least 7 days for a total cumulative dose of 1,500 mg of iron per course, or 15 mg/kg body weight up to a maximum of 1,000 mg intravenously as a single-dose treatment course. For patients weighing less than 50 kg, the recommended dosage is 15 mg/kg body weight intravenously in two doses separated by at least 7 days per course. Treatment may be repeated if IDA or iron deficiency in heart failure reoccurs.[4]

B. Applicable Statutory and Regulatory Framework

1. Legal Standards for Approval of an NDA

FDA's regulation of drug products is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 301 et seq.) and the Agency's implementing regulations codified in Title 21 of the Code of Federal Regulations (CFR). The FD&C Act makes it unlawful to market a new drug product without first obtaining an approved NDA or abbreviated new drug application (ANDA).[5] Before approving an application, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[6]

The statutory standard for determining whether a new drug is effective is "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which those experts could "fairly and responsibly" conclude that the drug is effective under the conditions of use suggested in its labeling.[7] "Substantial evidence" of effectiveness can also be established based on "data from one adequate and well-controlled clinical investigation and confirmatory evidence."[8] With respect to safety, applicants must provide evidence from "all methods reasonably applicable to show whether or not such drug is safe,"[9] including "pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant

[2] See Injectafer Prescribing Information (July 2013), at 1, 4, 6, and 14.
[3] Injectafer Prescribing Information (February 2020), at 1.
[4] Injectafer Prescribing Information (May 2023), at 1, 3.
[5] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505 of the FD&C Act).
[6] Section 505(b)(1) and (d) of the FD&C Act (21 U.S.C. 355(b)(1) and (d)).
[7] Section 505(d) of the FD&C Act. The characteristics of adequate and well-controlled studies are set forth in FDA regulations at 21 CFR 314.126. As stated in the regulation, these criteria were developed over a period of years and are recognized by the scientific community as the essential elements of well-controlled and credible investigations.
[8] Section 505(d) of the FD&C Act.
[9] Section 505(d)(1) of the FD&C Act (requiring FDA to deny an application lacking such information).

drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs."[10]

When analyzing whether a drug meets the standard for approval, FDA conducts a benefit-risk assessment that:

> takes into account the extensive evidence of safety and effectiveness submitted by a sponsor . . . as well as many other factors affecting the benefit risk assessment, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence.[11]

Only if FDA concludes that the product's benefit-risk profile is favorable will the Agency approve an NDA.[12] FDA must deny marketing approval if there is a lack of substantial evidence that the drug is effective, the results of safety testing fail to show that the drug is safe, or, on the basis of any other information before the Agency, there is insufficient evidence to determine whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling.[13]

2. Supplements

For most substantive changes to the conditions established in an approved NDA beyond the variations already provided for in the NDA, an application holder is required to submit a prior approval supplement and receive approval.[14] However, in the interest of public health, FDA's regulations permit certain labeling changes based on certain "newly acquired information" about an approved drug, such as added or strengthened safety information, to be distributed upon receipt by FDA of a changes being effected (CBE-0) supplement that includes the change.[15] "Newly acquired information" is defined to mean "data, analyses, or other information not

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[10] 21 CFR 314.50(d)(5)(vi)(a); see also § 314.50(d)(5)(iv) (description and analysis of "any other data or information relevant to an evaluation of the [drug's] safety and effectiveness . . . from any source . . . including information derived from clinical investigations . . . commercial marketing experience, reports in the scientific literature, and unpublished scientific papers"); 21 CFR 314.50(d)(2) (requirement for submission of nonclinical pharmacology and toxicology data).

[11] *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA V Implementation Plan – February 2013, Fiscal Years 2013-2017 at 1, 5-7, available at* https://www.fda.gov/media/84831/download. See also *Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA VI Implementation Plan (FY 2018-2022)* at 3-4, available at https://www.fda.gov/media/112570/download.

[12] See 21 CFR 314.105(c), which states "FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness." The information required to satisfy this requirement includes not only comprehensive safety and efficacy data, but also "an integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling." § 314.50(d)(5)(viii).

[13] Section 505(d)(1), (d)(2), (d)(4), and (d)(5) of the FD&C Act.

[14] § 314.70(b) (21 CFR 314.70(b)).

[15] § 314.70(c)(6)(iii).

previously submitted to the Agency."[16] Newly acquired information may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses); however, such information will qualify as newly acquired information under FDA regulations only if the studies, events, or analyses "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA."[17] Accordingly, nominally new information concerning risks of a materially similar type, severity, and frequency as those revealed in information previously evaluated by FDA is cumulative and not considered to be newly acquired information that could justify a CBE-0 supplement.

A CBE-0 supplement may be submitted to add or strengthen a contraindication, warning, precaution, or adverse reaction to reflect newly acquired information if "the evidence of a causal association satisfies the [relevant] standard for inclusion in the labeling."[18] If FDA does not subsequently approve the supplement, however, the Agency may order the application holder to cease distributing the drug with the labeling changes.[19] Historically, FDA has also accepted a prior approval supplement instead of a CBE-0 supplement, particularly where significant questions exist on whether to revise or how to modify existing drug labeling.

A prior approval supplement or CBE-0 supplement that proposes a safety-related change to product labeling must include all relevant data and information to demonstrate that the applicable statutory and regulatory standards have been met.[20] The applicant is expected to fully inform FDA of all material data and information related to the proposed safety-related labeling change and provide a justification for the proposed labeling change that describes the applicant's evaluation of such data and information (including strengths and limitations of the data from the various sources available to the applicant).

During the review process, FDA communicates with the applicant about scientific, medical, and procedural issues that may arise and engages in an iterative process involving a series of communications.[21] FDA may recommend substantive revisions to data and information described in draft labeling based on the Agency's evaluation and analysis of data submitted or otherwise available to the Agency. If FDA and the sponsor can reach agreement on the proposed labeling change (which may be modified by FDA or the applicant from the original submission), then FDA will approve the supplement. FDA will reject a supplement, however, if the proposed labeling change is false or misleading, or if it does "not comply with the requirements for labels and labeling in [21 CFR] part 201."[22] In such circumstances, FDA will send the applicant a "complete response letter."[23] A complete response letter reflects FDA's complete review of the data submitted and describes all of the specific deficiencies that the Agency has identified.[24]

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[16] See § 314.3(b) (21 CFR 314.3(b)).
[17] Id.
[18] § 314.70(c)(6)(iii)(A).
[19] § 314.70(c)(7).
[20] See, generally, sections 502 and 505(d) of the FD&C Act and §§ 201.57 and 314.70(b) and (c).
[21] All procedures and actions that apply to an application submitted to FDA generally apply to supplements (21 CFR 314.71(b) and (c)).
[22] §§ 314.125(b)(6) and (8) (21 CFR 314.125(b)(6) and (8)).
[23] § 314.110(a) (21 CFR 314.110(a)).
[24] § 314.110(a)(1) and (2).

FDA may determine that a sponsor's proposed labeling change is not warranted. For example, if in the Agency's judgment there is no "reasonable evidence of a causal association" between a drug and a clinically significant adverse reaction, FDA would decline to approve the addition of a warning about that risk.[25] If FDA determines that a proposed safety-related labeling change submitted is not warranted at the time under the relevant statutory and regulatory framework, the applicant may not resubmit a substantially similar proposed labeling change in a CBE-0 supplement unless newly acquired information "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA."[26]

3. Inclusion of Safety Information in FDA-Approved Labeling

In FDA-approved labeling, information about an adverse event is characterized as an adverse reaction when there is some basis to believe there is a causal relationship between the prescription drug and the occurrence of the adverse event.[27] A particular adverse reaction would ordinarily be described in either the Warnings and Precautions section or the Adverse Reactions section of the drug's FDA-approved labeling.

The Warnings and Precautions section must describe "clinically significant adverse reactions," other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur where "reasonable evidence of a causal association" between the drug and such hazards exists.[28] FDA regulations state that the labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[29]

The Adverse Reactions section describes "the overall adverse reaction profile of the drug."[30] FDA's regulations define an *adverse reaction*, for purposes of prescription drug labeling, as an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.[31] The threshold for including an adverse reaction in this section is lower than that for the Warnings and Precautions section: an adverse reaction must be listed if "some basis" exists "to believe there is a causal relationship between the drug and the occurrence of the adverse event."[32]

The Dosage and Administration section must describe "[a] concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the

[25] See § 201.57(c)(6)(i) (21 CFR 201.57(c)(6)(i)).
[26] See §§ 314.3(b) (definition of *newly acquired information*) and 314.70(c)(6)(iii). See also *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019) (". . . showing that [F]ederal law prohibited the drug manufacturer from adding a warning that would satisfy [S]tate law requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning required by [S]tate law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning").
[27] § 201.57(c)(7).
[28] § 201.57(c)(6)(i).
[29] Id.
[30] § 201.57(c)(7).
[31] Id.
[32] Id.

recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information."[33]

Under § 201.57(c)(1), a boxed warning may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury.[34] A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and other words that convey the general focus of information in the box.[35] A boxed warning briefly explains the risk(s) and refers to more detailed information in the Contraindications or Warnings and Precautions sections of the labeling.[36] A concise summary of this warning (with the heading "WARNING" and other words identifying the subject of the warning) must be included in the Highlights section in a box and in bold type.[37]

FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) (Warnings and Precautions Guidance) states that a boxed warning ordinarily is used to highlight one of the following situations:[38]

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug
  OR
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)
  OR
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under section 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).

The Warnings and Precautions Guidance (at 11-12) also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.

[33] § 201.57(a)(7); see also § 201.57(c)(3).
[34] See also 21 CFR 201.80(e).
[35] § 201.57(c)(1).
[36] Id.
[37] 21 CFR 201.56(d)(1) and § 201.57(a)(4).
[38] Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf.

II. DISCUSSION

A. Supplemental NDAs Based on FAIR-HF, CONFIRM-HF, and AFFIRM-AHF Trials

In your Petition, you request that FDA "[d]eny any Injectafer sNDAs for any labeling changes based on the FAIR-HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended to add or strengthen a contraindication, warning, precaution, or adverse reaction" (Petition at 2).

You raise several arguments with respect to the FAIR-HF and CONFIRM-HF studies. First, you argue that the "primary endpoints used in FAIR-HF and CONFIRM-HF are insufficient to support approval of an expanded indication" (Petition at 13). Regarding the FAIR-HF study, you assert that limitations include the use of the self-reported Patient Global Assessment (PGA) score instead of established quality of life measurements that are currently used in other studies (Petition at 6). Additionally, you state that dosing in the study was low and did not reflect contemporary use of high-dose IV iron (Petition at 6). You also note "limitations" regarding the CONFIRM-HF study, including the use of the 6-minute walk test instead of more objective endpoints such as peak oxygen consumption (VO_2) (Petition at 7, 14). You also raise concerns about what you characterize as small patient populations in each of these studies (Petition at 13).

Second, you claim that "the safety results in FAIR-HF and CONFIRM-HF do not provide sufficient information for FDA to evaluate the risk-benefit profile of Injectafer for any label extensions" (Petition at 14). Specifically, the Petition also expresses concerns regarding the lack of long-term safety or efficacy data beyond 24 or 52 weeks in these studies (Petition at 13) and the exclusion criterion for these studies, which the Petition claims "would encompass patients with pre-existing risk factors for hypophosphatemia" (Petition at 14).

Third, you claim that the FAIR-HF and CONFIRM-HF trials "reflect outdated clinical practice" (Petition at 15). The Petition also raises concerns about clinical trial integrity for the FAIR-HF and CONFIRM-HF studies, including outlier results at Eastern European trial sites (Petition at 6, 7, 12-13, 16).

Regarding the AFFIRM-AHF study, the Petition states that the study failed to meet its primary endpoint (Petition at 8). Additionally, due to what you characterize as the study's short exposure time, you assert that the occurrence of hypophosphatemia can be underestimated (Petition at 8-9). The Petition also states that the study was not "designed to investigate potential effects on serum phosphate or markers for bone turnover" (Petition at 8), and its study of a different patient population (hospitalized patients with LVEF $\leq$ 50%) means that it is not supportive of the FAIR-HF and CONFIRM-HF studies (which studied ambulatory patients with LVEF $\leq$ 40% and 45%, respectively) (Petition at 7, 16-17).

As a preliminary matter, FDA generally reviews a study in the context of a marketing application to determine whether it is appropriate and supportive, rather than making a priori decisions regarding the overall usefulness of the study. The appropriateness of a study would depend on the particular claims being made and the manner in which the study is referenced, among other

factors. While it is possible for a study to be so deficient in design or so poorly conducted as to be unusable, we do not believe that this is the case with these studies, as discussed further below.

Accordingly, we decline to comment on the overall appropriateness of the FAIR HF, CONFIRM HF, and AFFIRM AHF studies outside the context of a marketing application. However, because FDA today is approving a supplement expanding the approved indication for Injectafer to include treatment of iron deficiency in patients with symptomatic heart failure to improve exercise capacity, we do discuss the studies insofar as they relate to the expanded indication.

The primary efficacy endpoints in the FAIR-HF and CONFIRM-HF study are acceptable endpoints to evaluate the effect of Injectafer on symptom and function improvement in patients with iron deficiency and symptomatic heart failure. Regarding the FAIR-HF study, changes in self-reported PGA scores can provide information on a patient's perception of change in their condition and can be used in evaluating the treatment effect when combined with other endpoints. Additionally, while the dose used in the CONFIRM-HF study was different than the approved dose, the study's design nonetheless allows for determination of efficacy of the dosing regimen used in the study.

Regarding the CONFIRM-HF study, we believe that the 6-minute walk test is an appropriate endpoint. Benefits of the 6-minute walk test include that it can assess more sustained exercise ability, as opposed to assessing a subject's peak exercise ability. Both peak VO_2 and the 6-minute walk test can be used to assess efficacy, and in fact multiple product approvals have been based on studies with the 6-minute walk test as a primary endpoint.

Regarding the safety results in the FAIR-HF and CONFIRM-HF studies, we note that Injectafer is an approved drug with a known safety profile and considerable post-marketing experience. Safety data from FAIR-HF, CONFIRM-HF, and AFFIRM-AHF can be used to inform the overall benefit-risk assessment for Injectafer in the context of a particular supplemental application, and did inform the benefit-risk assessment of Injectafer to treat iron deficiency in patients with symptomatic heart failure to improve exercise capacity. Depending on the particular supplemental application, these data may not be the only data relied upon to evaluate the risk-benefit profile of Injectafer "for any label extensions." Instead, the totality of the safety data available (including from clinical trials, literature, and post-marketing data) may be considered to evaluate its safety.

Likewise, the standard of care and clinical trial integrity issues[39] you raised concerning the FAIR-HF and CONFIRM-HF studies do not demonstrate that the studies are so deficient in design or so poorly conducted as to be unusable. FDA is sensitive to evolving standards of care over time and how an investigational drug may perform relative to placebo under an evolved paradigm, and considers these issues as part of its review process.

[39] You did not include any information in your petition regarding alleged data integrity issues in the FAIR-HF and CONFIRM-HF studies other than to assert that Eastern Europe has "regional data integrity issues," and FDA is not aware of data integrity issues involving these studies. See Petition at 12. Accordingly, FDA's response does not address this part of your petition further.

Regarding your assertion that the AFFIRM-AHF study failed to meet its primary endpoint, we agree. However, this study can still be used to support safety information in the drug's labeling regarding the use of Injectafer in patients with iron deficiency and symptomatic heart failure. We do not believe that the duration, study design, or patient population negatively affect this approach.

Therefore, this part of your petition is granted in part and denied in part. It is granted in part to the extent that we generally agree that the primary efficacy results of AFFIRM-AHF cannot be used to inform a claim for improvement in exercise capacity. In all other respects, this part of your Petition is denied.

B. Discussion of Hypophosphatemia in Warnings and Precautions and Dosage and Administration Sections of Injectafer Prescribing Information

You also request that FDA "[s]trengthen Injectafer warnings and precautions and its dosage and administration in relation to severe and symptomatic hypophosphatemia and its consequences" (Petition at 2). You assert that the prescribing information is deficient because it does not include all patients who may be at risk for symptomatic hypophosphatemia, such as patients with osteoporosis and inflammatory bowel disease (Petition at 18). These risks are cited in the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) drug safety update and are supported by a comprehensive literature case review (Petition at 18). Additionally, the Petition states that the prescribing information does not include the risk of fractures (Petition at 18).

To support your request, the Petition discusses several reviews and studies that, you assert, demonstrate a causal relationship between Injectafer and hypophosphatemia. You first reference the European Medicines Agency's (EMA) review of the risk of hypophosphatemic osteomalacia for several IV iron products. The EMA concluded that a causal relationship between ferric carboxymaltose and hypophosphatemic osteomalacia is "at least a reasonable possibility" and recommended updating product information for ferric carboxymaltose products (Petition at 9).[40] Moreover, you explain that, after EMA's recommendations were published, MHRA issued a drug safety update that stated, among other things:

> [Injectafer] is known to be commonly associated with hypophosphatemia . . . cases have been reported of symptomatic hypophosphataemia leading to infrequent reports of hypophosphataemic osteomalacia and fractures in patients with existing risk factors and following prolonged exposure to high doses – some cases required clinical intervention, including surgery . . . advise patients to seek medical advice if they experience symptoms indicative of hypophosphataemia, including new musculoskeletal symptoms or worsening of tiredness – be aware these symptoms may be confused with those of iron deficiency anaemia . . . if hypophosphataemia persists, re-evaluate treatment with ferric carboxymaltose.

[40] Annex I: Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s), available at https://www.ema.europa.eu/en/documents/psusa/iron-parenteral-preparations-except-iron-dextrancmdh-scientific-conclusions-grounds-variation/00010236/202001_en.pdf (*see also* Petition, Exhibit L).

(Petition at 9-10).[41]

The Petition asserts that randomized clinical trials further support these findings (Petition at 10). You state that the FIRM trial, "a randomized, multicenter, double-blinded, controlled, noninferiority trial, compared the safety and efficacy of a single FDA-approved course of IV ferumoxytol versus Injectafer for the treatment of iron deficiency anemia" (Petition at 10). The trial found that "[t]he incidence of severe hypophosphatemia (<2.0 mg/dl) and extreme hypophosphatemia (<1.3 mg/dl) was significantly higher in the [Injectafer] group versus the ferumoxytol group (<2.0 mg/dl, 50.8% vs. 0.9%; <1.3 mg/dl, 10.0% vs. 0.0%; P < 0.001)."[42]

The Petition also discusses the PHOSPHARE trials, which "consisted of two identically designed, open-label, randomized clinical trials" (Petition at 10-11). The Petition states that the PHOSPHARE trials "compare[d] the incidence, severity, and mechanisms of hypophosphatemia, and effects on biochemical biomarkers of mineral and bone homeostasis of treatment with iron isomaltoside/ferric derisomalose or Injectafer in patients with iron deficiency anemia" (Petition at 11). The trial found that:

> The incidence of hypophosphatemia at any time from baseline to day 35 was significantly lower among patients treated with iron isomaltoside/ferric derisomaltose than with Injectafer (Trial A: 7.9% vs 75.0% [adjusted rate difference, –67.0% {95% CI, –77.4% to –51.5%}], P < .001; Trial B: 8.1% vs 73.7% [adjusted rate difference, –65.8% {95% CI, –76.6% to –49.8%}], P < .001). In fact, by day 7 of both trials, the prevalence of hypophosphatemia was significantly lower in patients treated with iron isomaltoside/ferric derisomaltose than Injectafer (pooled analysis: 3.3% vs 33.6 %), despite the Injectafer group having received only 750 mg of iron by that time vs 1000 mg in the iron derisomaltose group. Moreover, "[s]evere hypophosphatemia (serum phosphate ≤1.0 mg/dL) was not observed in iron isomaltoside[/ferric derisomaltose]-treated patients, but developed in 11.3% of [Injectafer]-treated patients in the pooled analysis (P < .001)."

(Petition at 11).[43]

Moreover, the Petition references data from the same trial indicating that Injectafer-induced hypophosphatemia can occur after a single dose (Petition at 17).[44] The labeling changes proposed in the Petition would expand recommended serum phosphate monitoring to include all patients receiving Injectafer and would specify the timing of serum phosphate monitoring. Additionally, the proposed revisions would advise against administering Injectafer to patients with one or more risk factors for hypophosphatemia. The Petition also proposes mentioning that hypophosphatemic osteomalacia and fractures have been reported in patients at risk of low serum

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[41] *Quoting* MHRA, Drug Safety Update, Ferric carboxymaltose (Ferinject▼): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures (Nov. 16, 2020), available at https://www.gov.uk/drug-safety-update/ferric-carboxymaltose-ferinject-risk-of-symptomatic-hypophosphataemia-leading-to-osteomalacia-and-fractures (*see also* Petition, Exhibit M).

[42] M. Wolf et al., Randomized trial of intravenous iron-induced hypophosphatemia, JCI INSIGHT, Dec. 2018, at 2 (*see also* Petition, Exhibit N).

[43] *Quoting* M. Wolf et al., Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials, 323 JAMA 432, 435 (2020) (*see also* Petition, Exhibit O).

[44] Id.

phosphate, that lower serum phosphate and active vitamin D on day 7 after a single treatment have been identified as independent predictors of hypophosphatemia lasting at least 5 weeks, and advising against administering to patients with one or more risk factors for hypophosphatemia. The proposal would revise the list of risk factors to include inflammatory bowel disease and osteoporosis. Other conforming changes are proposed (Petition at 18-19).

Lastly, the Petition requests that FDA either add a boxed warning to the prescribing information or issue a "dear doctor" letter (Petition at 19).

FDA recognizes that several publications have reported a higher risk of hypophosphatemia with Injectafer compared to other iron replacement products.[45] Based on FDA's own evaluation of the evidence, the Agency has concluded that there is reasonable evidence of a causal association between use of Injectafer and serious symptomatic hypophosphatemia, including hypophosphatemic osteomalacia. We also agree that some studies demonstrate that Injectafer-induced hypophosphatemia can occur after a single dose. Additionally, we agree that risk factors include, among others, inflammatory bowel disease. However, we do not agree that osteoporosis is a risk factor for hypophosphatemia. Although osteoporosis has been reported as a pre-existing condition in some patients with hypophosphatemic osteomalacia, there is no evident plausible biological mechanism by which osteoporosis increases the risk of hypophosphatemia.

We note that the risk of hypophosphatemia and hypophosphatemic osteomalacia are already reflected in the current prescribing information. However, in light of continued reports of hypophosphatemia and hypophosphatemic osteomalacia associated with the use of Injectafer and other safety information available to the Agency, FDA agrees that the prescribing information should be revised to include additional information regarding these risks. As part of the supplement we are approving today, we have approved revisions to the prescribing information to strengthen the discussion in the Warnings and Precautions section regarding hypophosphatemic osteomalacia and fractures as potential long-term complications, and to include inflammatory bowel disease among the risk factors for serious symptomatic hypophosphatemia.

[45] See N.F. Adkinson et al., Comparative safety of intravenous Ferumoxytol versus Ferric Carboxymaltose for the Treatment of Iron Deficiency Anemia: rationale and study design of a randomized double-blind study with a focus on acute hypersensitivity reactions, J Blood Med, 8, 155-163 (2017); G. Anand and C. Schmid, Severe hypophosphataemia after intravenous iron administration. BMJ Case Rep (2017); P. Bager et al., Drug-specific hypophosphatemia and hypersensitivity reactions following different intravenous iron infusions. Br J Clin Pharmacol, 83(5), 1118-1125 (2017); A. Blazevic et al., Severe hypophosphataemia after intravenous iron administration. Neth J Med, 72(1), 49-53 (2014); J. A. Glaspy et al., Hypophosphatemia Associated with Intravenous Iron Therapies for Iron Deficiency Anemia: A Systematic Literature Review. Ther Clin Risk Manag, 16, 245-259 (2020); L. L. Huang et al., A controlled study of the effects of ferric carboxymaltose on bone and haematinic biomarkers in chronic kidney disease and pregnancy. Nephrol Dial Transplant, 33(9), 1628-1635 (2018); K. Klein et al., Severe FGF23-based hypophosphataemic osteomalacia due to ferric carboxymaltose administration. BMJ Case Rep (2018); L. Y. Mani et al., Severe hypophosphatemia after intravenous administration of iron carboxymaltose in a stable renal transplant recipient. Transplantation, 90(7), 804-805 (2010); B. Schaefer et al., Choice of High-Dose Intravenous Iron Preparation Determines Hypophosphatemia Risk. PLoS One, 11(12) (2016); M. Wolf et al. (2018); M. Wolf et al., Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. J Bone Miner Res, 28(8), 1793-1803 (2013); and H. Zoller et al., Iron-induced hypophosphatemia: an emerging complication. Curr Opin Nephrol Hypertens, 26(4), 266-275 (2017).

FDA does not believe that the risks of hypophosphatemia necessitate the inclusion of a boxed warning in the prescribing information for Injectafer at this time. The current prescribing information already discusses hypophosphatemia in several sections, including the Highlights of Prescribing Information, Warnings and Precautions, and Adverse Reactions sections.[46] The existing discussion in the prescribing information, along with the revisions described above, provide sufficient details regarding the risks of hypophosphatemia. These revisions to the Warnings and Precautions statement do not merit an FDA initiated safety communication to the public, such as the Petition's request for a "dear doctor" letter.

Finally, we note that on January 11, 2023, you submitted a supplement to this Petition with information from recent publications that you assert support and complement the arguments in the Petition (Supplement at 1). The supplement first discusses a November 2022 publication from Dr. Milton Packer, which, according to the supplement, raises concerns about the lack of benefit in heart failure patients with nonischemic etiology, as well as what you describe as "the product-specific tendency of Injectafer" to increase fibroblast growth factor 23 (FGF23), leading to a risk of severe hypophosphatemia and potential risk of pathophysiological effects on the heart, including a tendency to cause hypertrophy (Supplement at 1-3).[47]

The supplement next discusses the IRONMAN trial published in November 2022. You state that the IRONMAN trial 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, and also that there was a homogenous risk reduction across subgroups. You compare these results to the AFFIRM-AHF trial, which you assert found a lack of numerical benefit on cardiovascular (CV) death for Injectafer (Supplement at 3-5).[48]

AFFIRM-AHF randomized 1132 patients with iron deficiency and heart failure with reduced LVEF to Injectafer or placebo and demonstrated a rate ratio of 0.79 (0.62, 1.01), p=0.059, for the primary composite endpoint of recurrent hospitalization for heart failure (HHF) and CV death up to 52 weeks after randomization. There was no difference in CV death between the two groups (77 [14%] of 558 in the Injectafer group *vs* 78 [14%] in the placebo group; hazard ratio 0·96, 95% CI 0·70–1·32, p=0·81). The IRONMAN trial of ferric derisomaltose[49] was a prospective, randomized, open-label, blinded-endpoint trial that randomized 1137 patients with iron deficiency and HF with reduced LVEF and demonstrated a RR of 0·82 [95% CI 0·66 to 1·02], p=0·070 for the primary endpoint of recurrent HHF and CV death. The primary results of IRONMAN are consistent with the primary results of AFFIRM-AHF and do not support a hypothesis of worsening heart failure with intravenous iron replacement products.

The information in your supplement does not alter our conclusions above. As discussed above, the risk of hypophosphatemia is already discussed in the Injectafer prescribing information, and we have agreed that the revisions described above are appropriate. Additionally, the proposed

[46] Injectafer Prescribing Information (May 2023), at 1, 4-7.
[47] *Citing* 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.
[48] *Citing* 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.
[49] Kalra et al.

possibility of elevated levels of FGF23 leading to pathophysiological effects on the heart is hypothetical and is not supported by the AFFIRM-AHF and IRONMAN trials, which do not demonstrate worsening heart failure with intravenous iron replacement products. The totality of the information available to the Agency supports the indications described in the Injectafer prescribing information as of this writing.

Therefore, this part of your petition is granted in part and denied in part. It is granted to the extent that FDA has approved certain revisions to the Warnings and Precautions section of the Injectafer prescribing information. In all other respects, this part of your Petition is denied.

C. Future Expanded or Additional Indications for Injectafer

The Petition's third request is that FDA "[r]equire 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" (Petition at 2). The Petition states that "FDA should not be able to determine whether the benefits of Injectafer outweigh its risks in the absence of adequate and well-controlled studies that specifically assess hypophosphatemia in the intended patient population" (Petition at 20). Given the risks of hypophosphatemia and the availability of alternative IV iron replacement products, you assert, the uncertainties regarding the risk-benefit profile of Injectafer are not tolerable (Petition at 20). We understand this request to ask FDA to require any potential future expanded or additional indication for Injectafer to be based on well-controlled clinical studies and that the risks of severe and symptomatic hypophosphatemia and its consequences should be assessed in FDA's review of marketing applications for this product.

As discussed above, the statutory standard for determining whether a new drug is effective is "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which those experts could "fairly and responsibly" conclude that the drug is effective under the conditions of use suggested in its labeling.[50] The adequacy of a study is generally determined in the context of a given application, so it would not be appropriate to determine outside of an application that a study cannot be used. However, we generally agree that adequate and well-controlled studies are needed to support a new indication for a drug.

FDA also notes that hypophosphatemia is a known risk for Injectafer, as it is currently described in the Injectafer prescribing information.[51] Therefore, the safety information needed to support a new indication would be determined within the context of a given marketing application.

Therefore, this part of your petition is granted in part to the extent you are asking that the risk of severe and symptomatic hypophosphatemia be assessed in FDA's review of marketing applications for Injectafer. This part of your petition is denied to the extent that you are asking FDA to determine which clinical studies are needed to support any new indication for Injectafer.

[50] See *supra* note 7.
[51] See *supra* note 46.

III. CONCLUSION

For the reasons described in this response, the Petition is granted in part and denied in part.

Sincerely,

Douglas C. Throckmorton -S

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Patrizia Cavazzoni, M.D.
Director
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