CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208551Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208551 (S-0000)
Priority or Standard	Standard
Submit Date(s)	June 25, 2015
Received Date(s)	June 25, 2015
PDUFA Goal Date	April 25, 2016
Division / Office	DHP/OHOP
Reviewer Name(s)	Min Lu, M.D., M.P.H.
Review Completion Date	March 17, 2016
Established Name	Ferric Pyrophosphate Citrate
(Proposed) Trade Name	Triferic Powder Packet
Therapeutic Class	Iron via Hemodialysate
Applicant	Rockwell Medical, Inc.
Formulation(s)	272 mg iron (III) per powder packet
Dosing Regimen	2 μM iron (110 μg iron per L of dialysate)
Indication(s)	For the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).
Intended Population(s)	Adult patients with hemodialysis-dependent chronic kidney disease

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical perspective, this reviewer recommends approval for this application.

1.2 Risk Benefit Assessment

Triferic powder packet is a new dosage form for the same indication as this sponsor's approved Triferic Solution under NDA 206317. This new dosage form contains 272 mg iron(III) per packet for addition to 25 gallons of bicarbonate concentrate to achieve a concentration of Triferic iron (III) in the final hemodialysate of 2 μM (110 mcg/L), which is the same iron concentration in the final hemodialysate provided by Triferic Solution. Triferic powder package is intended to be used in dialysis center to prepare master batches of dialysate for use in multiple patients. Risk benefit analysis assessment of Triferic powder is the same as for the approved Triferic solution under NDA 206317. See clinical review for NDA 206317 (Min Lu, dated 12/29/14) for detailed information.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant has two deferred pediatric studies under PMRs under NDA 206317 to meet the requirements of Pediatric Research Equity Act (PREA) for Triferic Solution (Approval Letter dated 1/23/2015).

PMR 2853-1
Complete the trial and submit the final report for the pediatric pharmacokinetic trial entitled "*Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis.*"
Final Protocol Submission: 03/31/2015
Trial Completion: 02/28/2017
Final Report Submission: 06/30/2017

PMR 2853-2
Efficacy and safety trial of Triferic via hemodialysate in pediatric patients aged less than 18 years with hemodialysis-dependent chronic kidney disease.
Final Protocol Submission: 03/31/2018
Trial Completion: 07/31/2020
Final Report Submission: 12/31/2020

The sponsor revised the pediatric study plan under NDA 206317 to include the (b) (4) powder packet dosage form in addition to the solution formulation in the proposed efficacy and safety pediatric study to be used at one or two pediatric hemodialysis units. The sponsor believes that the (b) (4) powder packet is not likely to be used extensively in pediatric hemodialysis units because of the smaller numbers of patients served as compared to adult hemodialysis units. FDA found the pediatric study plan acceptable (Pediatric Study Plan- Initial Agreement Letter for Triferic™ Powder dated 9/22/2015 under IND 51,290).

The approval of Triferic Powder Packet should include the same PMRs as for the Triferic Solution.

2 Introduction and Regulatory Background

2.1 Product Information

Triferic (ferric pyrophosphate citrate) powder is a slightly yellow-green powder, packaged in paper, polyethylene and aluminum foil packets, each containing 272.0 mg of iron (III). One Triferic powder packet is to be added to 25 gallons (94.6 liters) of master bicarbonate mix.

2.2 Tables of Currently Available Treatments for Proposed Indications

Current available treatment for iron deficiency anemia includes oral iron products and intravenous iron products. The approved intravenous iron products in the U.S. include Iron dextran (INFeD and Dexferrum), Ferrlecit, Venofer, Feraheme, and Injectafer. Only iron dextrans and Injectafer have been approved for a broad population and others have been approved for CKD population only. Triferic Solution was approved on January 23, 2015 for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). The approved populations, dose regimens and main safety concerns for these iron products are shown in the table below.

Table 1. Currently Approved Iron Products in US

Chemical name	Iron Dextran (INFeD, Dexferrum)	Ferrlecit (Sodium Ferric gluconate complex)	Venofer (Iron Sucrose)	Feraheme (ferumoxytol)	Injectafer (ferric carboxymaltose)	Triferic Solution (ferric pyrophosphate citrate)
Year of first U.S. approval	1974	1999 (marketed in Europe since 1950's)	2000 (marketed in Europe since 1950's)	2009	2013	2015
Indicated population	General patient population patients	Patients with HDD-CKD	Patients with CKD	Patients with CKD	General patient population and patients with NDD-CKD	Patients with HDD-CKD
Safety	Box warning for anaphylactic-type reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions	Boxed Warning for serious hypersensitivity/anaphylaxis reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions

Dose regimen	IV 100 mg daily until the calculated total amount required has been reached.	IV 125 mg x 8 doses at consecutive dialysis session	IV 100 mg x 10; IV 200 mg x 5 doses; IV 300 mg x 2 doses and 400 mg	IV 510 mg x 2 doses 3 to 8 days apart. Infusion only	IV 750 mg x 2 doses separated by at least 7 days.	Via dialysate: 27.2 mg iron(III) per vial added to 2.5 gallons of bicarbonate concentrate to achieve a final concentration of 2 μM (110 mcg/L) in the final hemodialysate.

2.3 Availability of Proposed Active Ingredient in the United States

Triferic Solution was approved in the U.S. on January 23, 2015. There are five intravenous iron products available in the U.S. as shown in Table 1 above. Iron has been considered as the active ingredient for all iron products.

2.4 Important Safety Issues with Consideration to Related Drugs

Intravenous iron products have been associated with anaphylactic-type reactions. Iron dextran (INFeD and Dexferrum) and Feraheme have a Boxed Warning for serious hypersensitivity/anaphylaxis reactions. Ferrlecit, Venofer, Injectafer, and Triferic solution have hypersensitivity reactions described under WARNINGS and PRECAUTIONS.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor submitted Triferic powder packet as a new packaging conformation, rather than as a new dosage form, as CMC supplement under NDA 206317 on February 2, 2015. A Refuse to File Letter was issued by the Agency on April 1, 2015 stating that the powder packet was a new dosage form requiring a new NDA. A Pre-NDA meeting was held between the Agency and the sponsor on June 12, 2015 to discuss the proper filing requirement for the powder dosage form.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

N/A. No clinical trials have been conducted for this NDA application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC review is pending.

5 Sources of Clinical Data

There were no clinical data submitted for review under this NDA. The sponsor cross referenced the NDA 206317 for all clinical data. See clinical review for NDA 206317 (Min Lu, dated 12/29/14) for detailed information.

6 Review of Efficacy

There were no clinical efficacy data submitted for review under this NDA. The sponsor cross referenced the NDA 206317 for all efficacy data. See clinical review for NDA 206317 (Min Lu, dated 12/29/14) for detailed efficacy information for Triferic.

7 Review of Safety

There were no clinical safety data submitted for review under this NDA. The sponsor cross referenced the NDA 206317 for all safety data. See clinical review for NDA 206317 (Min Lu, dated 12/29/14) for detailed safety information for Trferic.

8. Postmarket Experience

Based on the Periodic Adverse Drug Experience Report #4 submitted February 10, 2016, Triferic was commercially launched on September 8, 2015; as of December 31, 2015 there were 720 patient days of exposure to Triferic based on commercial sales; there have been no reportable cases or new adverse events reported during the previous 3 months. FDA FAERS search on February 24, 2016 by OSE showed no case of hypersensitivity reactions were reported since its approval on January 23, 2015.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

Triferic Powder Packet information should be combined into Triferic Solution label under NDA 206317 as a single label for Triferic products. Under Section 2 DOSAGE and ADMINISTRATION, a product comparison table is recommend and it should include dilution instructions for the 5 mL Triferic Injection, the 50 mL Triferic Injection, and the proposed Triferic powder packet to provide clear dilution instructions for different dosage forms of Triferic to avoid confusion and medication errors.

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this submission.

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

/s/

MIN LU
03/24/2016

KATHY M ROBIE SUH
04/05/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208551 **Applicant:** Rockwell Medical, Inc. **Stamp Date:** June 25, 2015

Drug Name: Triferic (ferric pyrophosphate citrate) powder, (b) (4) package **NDA/BLA Type:** S-0000

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			Cross-reference to NDA 206317
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			Cross-reference to NDA 206317
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			Cross-reference to NDA 206317
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			Cross-reference to NDA 206317
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			Cross-reference to NDA 206317
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			Cross-reference to NDA 206317
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			Cross-reference to NDA 206317
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Cross-reference to NDA 206317
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)*
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			x	Cross-reference to NDA 206317
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			x	Cross-reference to NDA 206317
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the			x	Cross-reference to NDA 206317 data

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N A	Comment
	Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	Cross-reference to NDA 206317
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Cross-reference to NDA 206317
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	Cross-reference to NDA 206317
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	Cross-reference to NDA 206317
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	Cross-reference to NDA 206317
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	Cross-reference to NDA 206317
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	Cross-reference to NDA 206317
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	Cross-reference to NDA 206317
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	Cross-reference to NDA 206317
25.	Have narrative summaries been submitted for all deaths and adverse event dropouts (and serious adverse events if requested by the Division)?			x	Cross-reference to NDA 206317
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or	x			Initial pediatric

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N A	Comment
	provided documentation for a waiver and/or deferral?				plan
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	Cross-reference to NDA 206317
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	Cross-reference to NDA 206317 data
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	Cross-reference to NDA 206317
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	Cross-reference to NDA 206317
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	Cross-reference to NDA 206317
34.	Are all datasets to support the critical safety analyses available and complete?			x	Cross-reference to NDA 206317
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	Cross-reference to NDA 206317
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	Cross-reference to NDA 206317
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	Cross-reference to NDA 206317
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			x	Cross-reference to NDA 206317
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	Cross-reference to NDA 206317

* Ferric Pyrophosphate Citrate (FPC, Triferic) powder is a powder dosage form [redacted] (b) (4) packaged in foil pockets for [redacted] (b) (4) use. Each packet contains 272 mg iron to be added to 25 gallons bicarbonate concentrate to use for 10 doses.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

NA.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Min Lu, M.D., M.P.H.	/electronic signature/
Reviewing Medical Officer	Date
Kathy Robie-Suh, M.D., Ph.D.	/electronic signature/
Clinical Team Leader	Date

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

/s/

MIN LU
08/11/2015

KATHY M ROBIE SUH
08/11/2015