CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208551Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	14-Apr-2016
From	Tracey Rogers, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208-551
Type of Application	Type 3 NDA
Applicant	Rockwell Medical Inc.
Date of Receipt	25-June-2015
PDUFA Goal Date	25-Apr-2016
Proposed Proprietary Name	Triferic
Dosage forms / Strength	Powder for Hemodialysis/272 mg iron (III) per packet
Route of Administration	Hemodialysis
Proposed Indication(s)	Triferic (ferric pyrophosphate citrate; FPC) is intended for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).
Recommended:	**Approval**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Product (William Adams, Ph.D.); in Panorama, dated 29-Mar-2016
- Drug Substance (William Adams, Ph.D.); in Panorama, dated 29-Mar-2016
- Microbiology (Nandini Bhattacharya, Ph.D.); in DARRTS, dated 29-Mar-2016
- Manufacturing Facilities (Steve Hertz, Ph.D.); in Panorama, dated 29-Mar-2016
- Manufacturing Process (Diane Goll, Ph.D.); in Panorama, dated 29-Mar-2016
- Clinical (Min Lu, M.D., MPH); in DARRTS, dated 05-Apr-2016
- Clinical Pharmacology (Olanrewaju Okusanya, PharmD, MS); in DARRTS, dated 18-Mar-2016
- Pharmacology/Toxicology (Pedro Del Valle, Ph.D.); in DARRTS, dated 11-Apr-1
- DMEPA (Ebony Ayres, PharmD, BCPPS); memo, dated 19-Jan-6
- Quality Biopharmaceutics (Banu Zolnik, Ph.D.); in Panorama, dated 29-Mar-2016

1. Introduction

Triferic Powder (ferric pyrophosphate citrate; FPC) is intended for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). Rockwell Medical Inc. has submitted NDA 208-551 for a powder for hemodialysis formulation of Ferric Pyrophosphate Citrate (FPC). The application is a Type 3 NDA, referencing the solution formulation, Triferic solution (NDA 206-317).

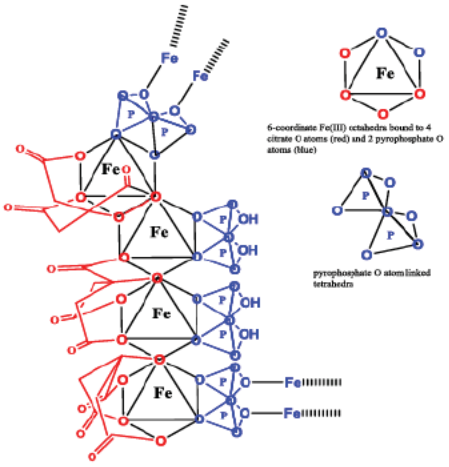
2. Background

Triferic powder is a packet (sachet) containing 272.0 mg iron (III) as FPC. One packet is to be admixed into 25 gallons (94.6 liters) of commercially available Liquid Bicarbonate Concentrate (LBC), then administered, via a dialysis machine (b) (4) as a dialysate containing of 110 µg iron (III)/L as FPC; this is the same iron concentration in the final dialysate provided by Triferic Solution

The current application relies on the Agency's determination of safety and efficacy for the Triferic Solution which has been previously approved for marketing under NDA 206317 on 23-Jan-2015.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 208551 is ferric pyrophosphate citrate.



Molecular Formula: $(Fe^{3+})_3 \bullet (C_6H_5O_7^{4-})_2 \bullet (P_2O_7^{4-})_2 * 2Na_2S0_4$ or $(Fe^{3+})_4 \bullet (C_6H_5O_7^{4-})_3 \bullet (P_2O_7^{4-})_3$

Ferric Pyrophosphate Citrate (USAN) is an octahedral coordination complex composed of ferric ion surrounded by pyrophosphate and citrate ligands with associated sodium and sulfate ions. Active moiety is stated to be four complexes in sequence sharing pyrophosphate and citrate ligands. Molecular structure of the active moiety is established by mass spectrometry, x-ray analysis, elemental analysis and ion content. Bulk drug material is a yellow to green (b) (4) powder and very soluble in water. This material is very (b) (4)

Currently, manufacture is by (b) (4). (b) (4) The synthesis process, process

controls and material specifications are adequate for the intended purpose and described in sufficient detail. The process includes [redacted] Packaging for storage and shipment provides [redacted] Currently manufacture and packaging is by [redacted] with release and stability testing performed by [redacted] Testing responsibilities for each contract lab are specified. Each proposed site has been found to meet GMP standards.

The proposed packaging system is [redacted] is justified by the stability studies. Packaging components and their acceptance specifications are described in sufficient detail and justified.

The primary stability study data and information is sufficient to support a re-test period of [redacted] months when at stored at [redacted] in the proposed packaging system. The post approval stability protocol and commitment are acceptable.

Triferic powder is a packet (sachet) containing 272.0 mg Fe(III) as FPC. One packet is to be admixed into 25 gallons (94.6 liters) of commercially available LBC, then administered, via a dialysis machine [redacted] as a hemodialysate containing of 110 µg Fe(III)/L as FPC. Triferic should not be added to the acid concentrate. Dosage of Triferic® is expressed as mg of iron(III). Hemodialysis solutions should be used within 24 hours of the preparation of the Triferic/LBC mixture. The applicant states that most U.S. dialysis centers prepare LBC mix in 50, 75 or 100 gallon increments to provide a master batch Triferic/LBC solution which is then used for multiple patient treatments.

4. Product Quality Microbiology

The drug product is a [redacted] powder. The overall manufacturing controls are adequate and the drug product is packaged into [redacted] packets [redacted]. The proposed compendial release tests and specifications are appropriate and have been verified suitable for use with the subject drug product. The final drug product specification has appropriate microbial limits and the reviewer anticipates that there is no risk for microbial proliferation during storage of the powdered drug substance or manufacture/filling of the drug product. During patient administration, the [redacted] drug product powder is added to [redacted] bicarbonate dialysis concentrate and the hemodialysis bicarbonate solution can be held for NMT 24 hours since preparation. Hold time studies for up to [redacted] following addition of the soluble ferric pyrophosphate (SFP) in the bicarbonate solution were performed to demonstrate that the ANSI/AAMI/ISO 11663 action levels for dialysate bioburden and endotoxins of 50 CFU/mL and 0.25 EU/mL, respectively, were met.

5. Biopharmaceutics

The proposed drug product in powder forms a solution upon mixing with the liquid bicarbonate. The Applicant is cross referencing the PK studies to NDA 206317, therefore biowaiver is not needed. There are no biopharmaceutics data or information in this NDA to be assessed.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends **approval** action for NDA 208-551 in that complete CMC information has been provided and issues raised during the review process have been resolved.

6. Clinical Pharmacology

No clinical pharmacology information was included in this application, and no changes to clinical pharmacology related portions of the package insert are proposed. The applicant cross-referenced their previously approved application NDA 206317.

The application is approvable from a clinical pharmacology perspective.

7. Non-Clinical Pharmacology/Toxicology

No new clinical data or nonclinical data was submitted with this application. The iron concentration in the final dialysate delivered to patients is the same as in the original NDA approval. The only material difference between (b) (4) powder packet and the packaging materials. The relevant nonclinical and clinical information are contained in NDA 206317.

8. Clinical/Statistical-Efficacy N/A

9. Safety N/A

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues

There are two PREA PMR's as follows:

- 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 report submission by June 30, 2017.
- Efficacy and safety trial of Triferic via hemodialysate in pediatric patients aged less than 18 years with hemodialysis-dependent chronic kidney disease. Final report submission by December 31, 2020.

13. Labeling

Final labeling was developed in discussions involving all review disciplines.

From the Clinical Review (M. Lu, 04/05/2015), the following recommendations were made:

> 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.

From the Clinical Pharmacology Review (O. Okusanya, 03/18/2016), the comments were made:

No changes to clinical pharmacology related portions of the package insert were proposed by the applicant. The reviewer has no labeling recommendations.

From the Pharmacology-Toxicology Review (P. Del Valle, 04/11/2016), the following comments were made:

Rockwell Medical Inc. cross referenced the annotated PI to the relevant sections of NDA 206317 and NDA 208551. The PI was edited for conversion to the PLLR format and the Applicant submitted final comments on the proposed USPI on March 22, 2016. No further edits to section 8 were necessary.

From DMEPA memo (E. Whaley, 04/11/2016), the following recommendations were made:

We acknowledge the Sponsor's request for reconsideration of the Agency's labeling recommendation for the Triferic 5 mL ampule. Per 21 CFR 201.2, the NDC number is requested but not required to appear on all labels and labeling. Additionally, 21 CFR 201.10(i) makes allowances for small labels and as such the NDC number is not required. Therefore, although NDC number can help with product identification, we agree with the Sponsor's request not to display the NDC number on the 5 mL ampule label and find the display of the NDC number on the pouch and carton labeling to be an acceptable alternative. However, if we identify any post- marketing cases related to unavailability of NDC number on the ampule label, we may consider additional regulatory action at that time.

From OPDP memo (J. Dvorsky, 02/16/2016), the following recommendations were made:

This memo is in response to your labeling consult request on July 13, 2015. We have reviewed the draft Package Insert for Triferic and do not have any comments at this time. This review is based upon the February 16, 2016, version of the label.

From Integrated Quality Assessment (CMC Review) (W. Adams, 03/29/2016), the following recommendations were made:

NDA 206317 is for *Triferic Solution*, 5mL of a sterile solution packaged in a LDPE ampule containing 5.44 mg Fe(III)/mL as FPC in Water for Injection, USP. One ampule is to be admixed into 2.5 gallons LBC at the clinic, then administered, via a dialysis machine (b) (4) as a hemodialysate containing of 110 µg Fe(III)/L as FPC. NDA 206317/suppl-02 approved the use of a 50cc (b) (4) ampule containing 50 mL of the same solution. The 50cc ampule is intended to be admixed with 25 gallons in LBC and administered in the same manner as the 5cc ampule. *NDA 208551* is for *Triferic Powder*, bulk FPC (DS) packaged into a paper (b) (4) /aluminum foil laminate packet (sachet) containing 272.0 mg Fe(III) as FPC with no excipients. One packet is intended to be admixed into 25 gallons of LBC, and then administered in the same manner as Triferic Solution.

The applicant states that most U.S. dialysis centers prepare LBC mix in 50, 75 or 100 gallon increments to provide a master batch Triferic/LBC solution which is then used for multiple patient treatments.
Response 1: This information has been incorporate into the package insert. The NDA notes that the master batch mix (Triferic/LBC) is prepared and a portion is delivered to the dialysis mixing machine.
S-004 Response: (b) (4)

Highlights
Indication & Usage: Acceptable
Dosage & Administration: Revisions in amendment S-013 are acceptable.
Full Prescribing Information
Section 1: Revisions in amendment S-013 are acceptable and DMEPA made no comment on the retained statement "iron replacement product indicated for …".
Section 2.1: Revisions in amendment S-013 are acceptable.
Section 3: Revisions in amendment S-013 are acceptable.
Section 11: Statements are acceptable.
Section 16.1: Revisions in amendment S-013 are acceptable. The absence of a separate NDC for individual 5cc ampules is acceptable to DMEPA (amendment S-015).
Section 16.2: Storage statement is supported by the study data in NDA sections 3.2.S.7 and 3.2.P.8.
Mfg For: Accepted in that this is the NDA holder.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

No new clinical or nonclinical data were provided with this submission, as no studies were conducted for this Type 3 NDA. The cross disciplinary team lead recommendation is for **approval**.

- **Risk Benefit Assessment**

Please refer to NDA 206317.

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/s/

TRACEY L ROGERS
04/14/2016

ANAMITRO BANERJEE
04/14/2016